

# ARCHIVES

## THE MIDDLESEX HOSPITAL

VOLUME VII

### Fifth Report

FROM THE

### Cancer Research Laboratories

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Middlesex Hospital, Cancer  
Research Laboratories

(ARCHIVES  
OF  
THE MIDDLESEX HOSPITAL  
VOLUME VII )

Fifth Report

FROM THE

Cancer Research Laboratories

EDITED FOR THE CANCER INVESTIGATION COMMITTEE

BY

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London

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## NOTICE.

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*In the following Pages, excepting where an asterisk (\*) is placed, or where the context makes it clear that such is not the case, EVERY DIAGNOSIS OF MALIGNANT DISEASE HAS BEEN MADE AS THE RESULT OF MICROSCOPIC EXAMINATION.*

W. S. L.-B.



# REPORTS

FROM THE

## CANCER RESEARCH LABORATORIES

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### TABULATED SYNOPSES OF THE POST-MORTEM EXAMINATIONS AND OPERATIONS IN CASES OF MALIGNANT DISEASE DURING THE YEAR 1905.

By THE DIRECTOR OF THE LABORATORIES  
and his ASSISTANTS.

IN the following tables are given the results of all cases of malignant disease—as determined by microscopical examination—which were investigated in the Cancer Research Laboratories during the year 1905. The material was derived partly from the post-mortem theatre and partly from the operating theatre. In all 182 cases (males 54, females 128) of malignant disease have been examined microscopically, a smaller number than usual owing to closure of the Hospital for two months for repairs. All of the above were in-patients. The total number of admissions to the Hospital as in-patients during 1905 was 3,147; viz., 1,475 males, and 1,672 females. In addition, 5 males and 22 females with malignant disease were admitted to the Electrical (Out-patient) Department for X-ray treatment. Histological examination was not made in these cases.

Besides the cases that have been mentioned, a certain number of patients were admitted (either to the general wards or to the special wards) in which the diagnosis of malignant disease was not made certain by histological examination. These are grouped in two classes according to the relative probability of accuracy in the diagnosis.

In the first group the diagnosis was founded on naked-eye appearances or on touch, but the patients were discharged unrelieved from Hospital at their own request, or else left the Hospital relieved after palliative operation (*e.g.*, cases of colotomy, gastrostomy, gastro-jejunostomy).

In the second group the diagnosis was made on clinical grounds alone.

## GROUP 1.

*Cases diagnosed as Malignant Disease on Evidence derived from the Naked-Eye Appearance or by Touch.*

Site.	1905.			1904.		
	Females.	Males.	Total.	Females.	Males.	Total.
Uterus ... ..	15	—	15	25	—	25
Breast ... ..	8	—	8	12	—	12
Rectum ... ..	1	4	5	5	9	14
Colon ... ..	—	1	1	3	2	5
Gall-bladder ... ..	1	—	1	1	—	1
Stomach ... ..	—	1	1	—	2	2
Tongue ... ..	1	1	2	—	3	3
Omentum ... ..	1	—	1	1	—	1
Ovary ... ..	1	—	1	2	—	2
Bladder ... ..	—	1	1	1	—	1
Rodent cancer ... ..	—	1	1	1	5	6
Parotid ... ..	1	—	1	—	—	—
Cervical glands ... ..	—	1	1	—	—	—
Mediastinum ... ..	—	1	1	—	—	—
Pancreas ... ..	1	—	1	—	—	—
Lip ... ..	—	—	—	—	2	2
Mouth and Jaw ... ..	1	—	1	1	5	6
Pharynx ... ..	—	—	—	—	1	1
Larynx ... ..	—	—	—	—	1	1
Penis and scrotum ... ..	—	—	—	—	3	3
Skin ... ..	—	—	—	—	4	4
Thyroid ... ..	—	—	—	1	—	1
Eye (melanotic sarcoma) ... ..	—	—	—	—	2	2
Bones (sarcoma) ... ..	—	—	—	1	2	3
Kidney (sarcoma) ... ..	—	—	—	—	1	1
Mesentery ... ..	—	—	—	—	1	1
Totals ... ..	31	11	42	54	43	97

# CANCER RESEARCH LABORATORIES.

3

## GROUP II.

*Cases diagnosed as Malignant Disease on Clinical Evidence alone.*

Site.	1905.			1904.		
	Females.	Males.	Total.	Females.	Males.	Total.
Stomach ... ..	4	5	9	4	4	8
Esophagus ... ..	1	2	3	—	5	5
Cecum ... ..	—	—	—	—	3	3
Colon ... ..	—	—	—	1	1	2
Lung ... ..	—	—	—	1	—	1
Liver ... ..	—	—	—	1	—	1
Totals ... ..	5	7	12	7	13	20

TABLE I.—

				Total.	21—25.		26—30.		31—35.		36—40.		41—45.		46—50.	
				M. F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
<b>CARCINOMA.</b>																
ALIMENTARY SYSTEM	Eyelid ...	...	Rodent	—	1	—	—	—	—	—	—	—	—	—	—	—
	Tongue ...	...	Squamous	4	1	—	—	—	—	—	—	—	—	—	1	—
	Palate ...	...	Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—
	Tonsil ...	...	Squamous	4	—	—	1	—	—	—	—	—	—	—	1	—
	Esophagus ...	...	Squamous	2	2	—	—	—	1	—	—	—	—	—	1	—
	Stomach, Cardiac end ...	...	Columnar	1	—	—	—	—	—	—	—	—	—	—	—	—
	" Middle ...	{	Spheroidal	1	—	—	—	—	—	—	—	—	—	—	—	—
			Columnar	1	—	—	—	—	—	—	—	—	—	—	—	—
	Duodenum ...	...	Spheroidal	—	1	—	1	—	—	—	—	—	—	—	—	—
	Cecum ...	...	...	—	1	—	—	—	—	—	—	—	—	—	—	—
URO-GENITAL SYSTEM.	Sigmoid Flexure ...	{	Transitional	1	—	—	—	—	—	—	—	—	—	—	—	—
			Columnar	1	1	—	—	—	—	—	—	—	—	—	—	1
	Rectum ...	...	Columnar	2	3	—	—	—	—	—	—	—	1	1	—	—
	Common bile-duct ...	...	Columnar	—	1	—	—	—	—	—	—	—	—	—	—	—
	Pancreas ...	...	Spheroidal	1	1	—	—	—	1	—	—	1	—	—	—	—
	Kidney ...	...	Transitional	—	1	—	—	—	—	—	—	—	—	—	—	—
	Bladder ...	...	Squamous	2	1	—	—	—	—	—	—	—	—	—	—	1
	Prostate ...	...	Spheroidal	1	—	—	—	—	—	—	—	—	—	—	—	—
	Cervix uteri ...	{	Spheroidal	—	1	—	—	—	—	—	1	—	—	—	—	—
			Columnar	—	7	—	—	1	—	—	2	—	1	—	—	1
			Squamous	—	18	—	—	—	2	—	1	—	2	—	—	2
	Vulva ...	...	Squamous	—	1	—	—	—	—	—	—	—	—	—	—	—
	Breast ...	...	Spheroidal	—	12	—	—	—	—	—	—	—	1	—	—	—
	Proliferating Cystadenoma ...	...	...	—	3	—	1	—	—	—	—	—	1	—	—	1
<b>SARCOMA.</b>																
Mixed-cell ...				1	—	—	—	—	—	—	—	—	—	—	—	—
Round-cell ...				3	5	—	—	1	2	Scapul.	—	—	Testis	Pylo-	—	—
								Kidney.	Ovary	pul-						
								Femur.	—	—						
Spindle-cell ...				1	1	—	—	—	—	—	—	—	—	—	Cæcum	—
Myeloid ...				1	—	Humerus.	—	—	—	—	—	—	—	—	—	—
Melanotic ...				—	3	—	—	—	—	Heel	—	—	—	—	—	—
Lymphosarcoma ...				1	—	Mediastinum.	—	—	—	—	—	—	—	—	—	—
Endothelioma ...				4	5	—	—	—	—	—	Breast	Liver	—	—	—	—
												Cervix.	2	1	2	2
												—	Tongue	Breas	—	—
												—	Esophagus.	Omen-	tum.	—
												—	—	—	—	—



### POST-MORTEM CASES.

[illegible]

TABLE II.—

		Total.	0—5.		6—10.		11—15.		16—20.		21—25.		26—30.		31—35.		36—40.			
		M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.	M. F.			
CARCINOMA.																				
Alimentary Canal.	Lip ... Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
	Tongue ... Squamous	6	—	—	—	—	—	—	—	—	—	—	—	—	—	—	1	—		
	Soft Palate Squamous	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
	Intestine ... Columnar	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Generative System	} Squamous	4	3	—	—	—	—	—	—	—	—	—	—	—	—	—	1 (cervix)	—		
		Breast {	Spheroidal	—	34	—	—	—	—	—	—	—	1	—	—	—	—	1	—	
Columnar	—		4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Other Sites ...	Squamous	3	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
RODENT CANCER ... ..		—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
SARCOMA.																				
Mixed-cell	... ..	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Round-cell	... ..	1	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Spindle-cell	... ..	4	3	—	—	1 (thigh)	1 (gum)	—	—	1 (femur)	—	—	—	—	—	—	—	—		
Fibro-sarcoma	... ..	—	1	—	—	1 (jaw)	—	—	—	—	—	—	—	—	—	—	—	—		
Myxo-sarcoma	... ..	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Endothelioma	... ..	1	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
		21	58	TOTAL NUMBER OF OPERATION CASES FOR MALIGNANT DISEASE ... ..															(Carcinoma—Males 15, Females 44) Sarcoma " 5, " 9 Endothelioma " 1, " 5	
NON-MALIGNANT.		7	18	1	—	—	—	1	—	—	—	3	—	2	2	—	1	2		
		28	76	TOTAL NUMBER OF OPERATION CASES EXAMINED IN CANCER RESEARCH LABORATORIES.																

## OPERATION CASES.

41—45.		46—50.		51—55.		56—60.		61—65.		66—70.		71—75.		76—80.		81—85.	
M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—
2	—	—	—	1	—	—	—	2	—	—	—	—	—	—	—	—	—
—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	1 (rec- tum)	—	1 (rec- tum)	—	—	—	—	—	—	—	—	—	—
—	—	—	—	1 (penis)	—	1 (penis)	1 (cer- vix)	—	—	—	—	1 (sero- tum)	—	—	—	1 (sero- tum)	1 (labium majus)
—	7	—	5	—	8	—	6	—	2	—	2	—	—	—	—	—	1
—	2	—	1	—	—	—	1	—	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	2 (leg, skin)	—	1 (skin)	—	—	—	—	—
—	1 (nose)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	1 (paro- tid)	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	—	—	1 (abd. wall)	—	—	—	—	—	—	—	—	—	—	1 (sep- tum nasi)	—	—	—
—	—	1 (abdo- men)	—	—	1 (breast)	—	1 (thigh)	1 (foot)	—	—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1 (paro- tid)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
—	1 (breast)	—	—	—	—	—	—	—	1 (breast)	—	—	—	—	—	—	—	—

1	4	1	3	—	—	—	—	1	3	—	—	—	—	—	—	—	—
---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---	---

TABLE III.

## SYNOPSIS OF POST-MORTEM CASES.

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnor- malities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
1	E.S. 100/05	F	64	Rodent cancer of left lower eyelid.	None.	Double broncho-pneumonia; tuberculosis of right lung; pleural adhesions on left side.	(i) Patent foramen ovale. (ii) Considerable emaciation.	(i) 22 Nov. '04. (ii) 30 May '05.
2	H.F.G. 50/05	M	46	Squamous cell carci- noma of tongue.	Sub-maxillary glands.	Double broncho-pneumonia. Aorta atheromatous.	(ii) Marked emacia- tion.	(i) 11 Feb. '05. (ii) 22 March '05.
3	T.B. 144/05	M	57	Squamous cell carci- noma of tongue.	Cervical glands.	Cystic adenomata of thyroid; gangrenous pneumonia.	(ii) Well nourished.	(i) 21 July '05. (ii) 29 Aug. '05.
4	E.T. 67/05	F	61	Squamous cell carci- noma of tongue.	Skin, cervical glands, epiglottic folds.	Laryngitis.	(ii) Emaciated.	(i) 17 March '05. (ii) 12 April '05.
5	A.M.C. 129/05	M	68	Squamous cell carci- noma of tongue. Squamous cell carci- noma of bladder.	None.	... ..	(ii) Well nourished.	(i) 4 May '05. (ii) 14 July '05.
6	G.M. 26/05	M	76	Squamous cell carci- noma of tongue.	Cervical glands.	Broncho-pneumonia and gan- grene of right lung, aeterna of left lung; marked atheroma of arteries	(ii) Distinct emacia- tion.	(i) 21 Dec. '04. (ii) 19 Feb. '05.
7	C.F. 163/05	M	56	Squamous cell carci- noma of palate (lym- phatic perithelioma).	Cervical and sub-maxillary glands.	... ..	(ii) Fairly nour- ished.	(i) 31 Aug. '05. (ii) 20 Oct. '05.



8	J.S. 188/05	M	27	Squamous cell carcinoma of right tonsil.	Liver, portal and cervical glands.	Broncho-pneumonia.	(ii) Much emaciation.	(i) 8 April '05. (ii) 21 Nov. '05.
9	J.B. 22/05	M	49	Squamous cell carcinoma of left tonsil.	Cervical glands, œsophagus.	Pigment calculi in gall bladder; œdema of larynx and lungs.	(ii) Slight emaciation.	(i) 4 Jan. '05. (ii) 9 Feb. '05.
10	J.F. 30/05	M	59	Squamous cell carcinoma of left tonsil.	Cervical glands.	Chronic interstitial nephritis.	(ii) Much emaciation.	(i) 6 Aug. '04. (ii) 23 Feb. '05.
11	M.N. 29/05	M	62	Squamous cell carcinoma of left tonsil.	Cervical glands.	Atheroma of aorta.	(ii) Much emaciation.	(i) 10 Jan. '05. (ii) 22 Feb. '05.
12	G.B. 156/05	M	60	Squamous cell carcinoma of œsophagus perforating left bronchus.	Bronchial glands.	Erosion of vertebrae.	(ii) Extreme emaciation. Hosp. p.m. 139.	(i) 25 Sept. '05. (ii) 6 Oct. '05.
13	S.B. 110/05	F	59	Squamous cell carcinoma of œsophagus.	None.	Peritonitis.	(ii) Emaciated. Hosp. p.m. 104.	(i) 20 April '05. (ii) 8 June '05. (iii) Gastrostomy.
14	A.D. 211/05	M	49	Squamous cell carcinoma of œsophagus ulcerating into trachea.	Vertebral glands.	...	(ii) Great emaciation. Hosp. p.m. 171.	(i) 24 Nov. '05. (ii) 20 Dec. '05. (iii) Gastrostomy.
15	C.B. 208/05	F	35	Squamous cell carcinoma of œsophagus.	Cervical glands.	...	(ii) Much emaciation.	(i) 7 Dec. '05. (ii) 18 Dec. '05.
16	W.F. 77/05	M	62	Columnar cell carcinoma of cardiac end of stomach.	Liver, mesenteric glands, peritoneum	Ascites.	(ii) Great emaciation. Hosp. p.m. 85.	(i) 20 March '05. (ii) 27 April '05.
17	H.W. 12/05	M	52	Spheroidal cell carcinoma of middle of stomach.	Cœliac and lumbar glands, transverse colon (adherent to stomach.)	Sub-diaphragmatic abscess.	(ii) Emaciation.	(i) 19 Jan. '05. (ii) 26 Jan. '05.
18	J.S. 104/05	M	55	Columnar cell carcinoma of stomach (small curvature).	Stomach, peritoneum.	Tuberculosis of mediastinal glands.	(ii) Body thin. Hosp. p.m. 103.	(i) 9 Feb. '05. (ii) 4 June '05.

TABLE III.—SYNOPSIS OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnor- malities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
19	A.L. 164/05	F	24	Spheroidal cell carci- noma of duodenum.	Liver, pancreas, omentum, retro-pe- ritoneal, mesenteric and lumbar glands.	... ..	(ii) Fairly nour- ished.	(i) 25 Sept. '05. (ii) 22 Oct. '05.
20	M.H. 212/05	F	64	Columnar cell carci- noma of cecum.	Liver, fallopian tube, peritoneum.	Old peritoneal adhesions.	(ii) Much emacia- tion. Hosp. p.m. 172.	(i) 20 Dec. '05. (ii) 21 Dec. '05. (iii) Laparotomy, 21 Dec. '05.
21	W.E.H. 43/05	M	59	Spheroidal cell carci- noma of sigmoid flexure.	None.	... ..	(ii) Body thin. Hosp. p.m. 45.	(i) 13 March '05. (ii) 17 March '05.
22	E.A.W. 122/05	F	50	Columnar cell carci- noma of sigmoid flexure.	None.	... ..	(ii) Well nourished.	(i) 30 May '05. (ii) 24 June '05. (iii) Cholecystectomy.
23	J.H. 121/05	M	57	Columnar cell carci- noma of sigmoid flexure.	Liver, lung, kid- ney.	... ..	(i) Patent foramen ovale. (ii) Emaciation. Much jaundice. Hosp. p.m. 119.	(i) 18 May '05. (ii) 25 June '05. (iii) Resection of gut, April '05.
24	L.S. 205/05	F	44	Columnar cell carci- noma of rectum.	Liver, lungs.	Left hydronephrosis.	(ii) Much emacia- tion.	(i) 19 June '05. (ii) 13 Dec. '05. (iii) Left inguinal cectomy.
25	A.B. 146/05	M	46	Rectum *	None.	... ..	(ii) Emaciation.	(i) 26 Jan. '05. (ii) 11 Sept. '05. (iii) Left inguinal cectomy.

\* This case is included on macroscopic grounds; micro-  
scopic examination of numerous specimens failed  
to demonstrate malignant disease.

26	E.W. 162/05	F	54	Columnar cell carcinoma of sigmoid extending to bladder.	None	Recto-vesical fistula.	(i) Fairly nourished. Hosp. p.m. 136.	(i) 18 Oct. '05. (ii) 19 Oct. '05.
27	R.K. 52/05	F	66	Columnar cell carcinoma of rectum.	None.	Peritonitis.	(i) Well nourished. Hosp. p.m. 53.	(i) 20 March '05. (ii) 22 March '05. (iii) Enterectomy, 21 March '05.
28	T.B. 210/05	M	72	Columnar cell carcinoma of rectum.	Liver.	Single gallstone.	... ..	(i) 22 Feb. '05. (ii) 19 Dec. '05.
29	E.S. 59/05	F	60	Columnar cell carcinoma of common bile duct.	None.	Gallstones. Peritonitis.	(ii) Well nourished. Jaundiced. Hosp. p.m. 67.	(i) 17 March '05. (ii) 5 April '05. (iii) Cholecystotomy.
30	C.B. 168/05	F	32	Spheroidal cell carcinoma of head of pancreas.	None.	Old peritoneal adhesions.	(ii) Extreme emaciation. Jaundice. Hosp. p.m. 140.	(i) 19 Sept. '05. (ii) 25 Oct. '05.
31	J.M. 6/05	M	43	Spheroidal cell carcinoma of pancreas.	Liver, stomach, cæcæ and lumbar glands.	... ..	(ii) Emaciated. Jaundiced.	(i) 18 Dec. '04. (ii) 12 Jan. '05. (iii) Exploratory, Dec. '04.
32	M.L. 84/05	F	58	Transitional cell carcinoma of pelvis of right kidney.	Liver, retro-peritoneal glands, right ureter.	Renal calculus.	(ii) Hosp. p.m. 91.	(i) 27 April '05. (ii) 9 May '05. (iii) Nephrolithotomy.
33	G.P. 99/05	F	48	Squamous cell carcinoma of urinary bladder.	Liver, abdominal glands.	Gallstones.	(ii) Hosp. p.m. 98.	(i) 18 May '05. (ii) 29 May '05.
34	C.D. 88/05	M	64	Squamous cell carcinoma of urinary bladder.	L y m p h a t i c glands.	Solitary gallstone, purulent cholecystitis; consecutive nephritis.	(ii) Much emaciated.	(i) 23 Dec. '04. (ii) 16 May '05.
35	H.H. 214/05	M	70	Squamous cell carcinoma of urinary bladder.	Prostate.	Consecutive nephritis.	(ii) Hosp. p.m. 179.	(i) 16 Dec. '05. (ii) 27 Dec. '05.

TABLE III.—SYNOPSIS OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Registrar Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnor- malities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
36	H.L. 45/05	M	71	Spheroidal cell carci- noma of prostate.	Lumbar and in- guinal glands, ure- ter.	Double hydronephrosis. Lungs, old tuberculosis.	(ii) Well nourished.	(i) 10 Dec. '04. (ii) 19 March '05.
37	S.R. 131/05	F	39	Spheroidal cell carci- noma of cervix uteri.	Pelvic glands.	Right pyonephrosis.	(ii) Extreme ema- ciation.	(i) 6 Jan. '05. (ii) 16 July '05.
38	A.N. 132/05	F	30	Columnar cell carci- noma of cervix uteri.	Lumbar and iliac glands.	... ..	(ii) Extreme ema- ciation.	(i) 8 April '05. (ii) 21 July '05.
39	E.B. 137/05	F	37	Columnar cell carci- noma of cervix uteri.	None.	Left pyonephrosis.	(ii) Much emacia- tion.	(i) 3 Dec. '04. (ii) 4 Aug. '05.
40	H.R. 133/05	F	40	Columnar cell carci- noma of cervix uteri.	None.	... ..	(ii) Well nourished.	(i) 27 March '03. (ii) 21 July '05.
41	M.S. 81/05	F	42	Columnar cell carci- noma of cervix uteri.	None.	General peritonitis. Hæmorrhage into right adrenal. Right hydronephrosis.	(ii) Well nourished.	(i) 24 June '03. (ii) 2 May '05.
42	E.C. 33/05	F	49	Columnar cell carci- noma of cervix uteri.	None.	Double hydronephrosis. Vesico-vaginal fistula.	(ii) Great emacia- tion.	(i) 19 March '04. (ii) 26 Feb. '05.
43	M.B. 138/05	F	53	Columnar cell carci- noma of cervix uteri.	None.	... ..	(ii) Much emacia- tion.	(i) 31 Aug. '05. (ii) 9 Aug. '05.
44	S.P. 60/05	F	62	Columnar cell carci- noma of cervix uteri.	None.	... ..	(ii) Well nourished.	(i) 25 March '05. (ii) 7 April '05.
45	E.M. 13/05	F	34	Squamous cell carci- noma of cervix uteri.	None.	Bronchocele. Right hydronephrosis.	(ii) Extremely ema- ciated.	(i) 21 Dec. '03. (ii) 25 Jan. '05.
46	E.C. 38/05	F	34	Squamous cell carci- noma of cervix uteri.	Liver, lumbar glands.	Double hydronephrosis. Ascites.	(ii) Well nourished.	(i) 11 Feb. '05. (ii) 4 March '05.



47	E.B. 141/05	F	38	Squamous cell carcinoma of cervix uteri.	None.	Left hydronephrosis.	(i) Much emaciation.	(i) 8 May '05. (ii) 12 Aug. '05.
48	M.E.M. 199/05	F	41	Squamous cell carcinoma of cervix uteri.	None.	Double hydronephrosis.	(ii) Much emaciation.	(i) 25 Sept. '05. (ii) 5 Dec. '05.
49	A.K. 143/05	F	43	Squamous cell carcinoma of cervix uteri.	Ovary.	...	(ii) Much emaciation.	(i) 29 July '05. (ii) 25 Aug. '05.
50	F.A.M. 118/05	F	47	Squamous cell carcinoma of cervix uteri.	None.	...	(ii) Well nourished.	(i) 4 Sept. '05. (ii) 13 Sept. '05.
51	M.H. 187/05	F	50	Squamous cell carcinoma of cervix uteri.	None.	Double pyonephrosis.	(i) Patent foramen ovale. (ii) Much emaciation.	(i) 21 Nov. '04 (ii) 21 Nov. '05.
52	E.H. 3/05	F	52	Squamous cell carcinoma of cervix uteri.	Punctus uteri, broad ligaments, spleen.	Hydronephrosis (right side), old pulmonary tuberculosis.	(ii) Well nourished.	(i) 16 Dec. '04. (ii) 6 Jan. '05.
53	C.R. 127/05	F	53	Squamous cell carcinoma of cervix uteri.	None.	Pericardial adhesions and effusion. Double hydronephrosis. Ascites.	(ii) Well nourished.	(i) 10 Feb. '05. (ii) 9 July '05.
54	M.A.M. 213/05	F	55	Squamous cell carcinoma of cervix uteri.	Blac and lumbar glands.	Double pyonephrosis.	(ii) Fairly nourished.	(i) 7 Aug. '05. (ii) 22 Dec. '05.
55	M.H. 290/05	F	55	Squamous cell carcinoma of cervix uteri.	Liver, inguinal and bronchial glands	Double hydronephrosis.	(ii) Much emaciation.	(i) 29 June '05. (ii) 8 Dec. '05.
56	E.O. 153/05	F	57	Squamous cell carcinoma of cervix uteri.	None.	Left pyonephrosis.	(ii) Some emaciation.	(i) 25 July '05. (ii) 2 Oct. '05.
57	M.T. 160/05	F	57	Squamous cell carcinoma of cervix uteri.	None.	...	(ii) Emaciated.	(i) 2 Aug. '05. (ii) 17 Oct. '05.
58	M.P.E. 23/05	F	59	Squamous cell carcinoma of cervix uteri.	None.	Gallstone. Double hydronephrosis.	(ii) Slight emaciation.	(i) 23 Feb. '04. (ii) 8 Feb. '05. (ii) Vaginal hysterectomy.

TABLE III.—SYNOPSIS OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnor- malities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
59	S.B. 179/05	F	63	Squamous cell carcinoma of cervix uteri.	Inguinal glands.	Gallstones. Chronic interstitial nephritis.	(i) Emaciated. (ii)	(i) 25 June '05. (ii) 5 Nov. '05.
60	J.J. 166/05	F	65	Squamous cell carcinoma of cervix uteri.	None.	Uterine fibroid.	(ii) Fairly nourished.	(i) 23 Oct. '05. (ii) 24 Oct. '05.
61	D.W. 170/05	F	71	Squamous cell carcinoma of cervix uteri.	None.	... ..	(ii) Fairly nourished.	(i) 16 Dec. '04. (ii) 27 Oct. '05.
62	M.M. 189/05	F	73	Squamous cell carcinoma of cervix uteri.	None.	Gallstones. Left hydronephrosis.	(ii) Slight emaciation.	(i) 27 Oct. '05. (ii) 21 Nov. '05.
63	M.Q. 151/05	F	69	Squamous cell carcinoma of vulva.	Inguinal glands.*	Old pulmonary tuberculosis.	(ii) Thin.	(i) 10 Jan. '05. (ii) 22 Sept. '05.
64	S.W. 58/05	F	43	Spheroidal cell carcinoma of left breast.	Cervical glands.	Extreme rickets. Chronic mastitis.	(ii) Moderate emaciation.	(i) 8 Feb. '05. (ii) 4 April '05. (iii) Amputation of breast, Nov. 1900.
65	E.H. 32/05	F	52	Spheroidal cell carcinoma of left breast.	Axillary and supra-clavicular glands, orbital peritoneum, sphenoid, liver.	Fatty heart. Chronic interstitial nephritis.	(ii) Well nourished.	(i) 21 Jan. '05. (ii) 25 Feb. '05.
66	J.H. 35/05	F	53	Spheroidal cell carcinoma of left breast.	Liver.	Acute lobar pneumonia (left side).	(ii) Emaciation.	(i) 5 Nov. '04. (ii) 27 Feb. '05.
67	E.H. 135/05	F	60	Spheroidal cell carcinoma of right breast.	Omentum, liver, diaphragmatic peritoneum.	Gallstones.	(ii) Much emaciation.	(i) 13 June '05. (ii) 27 July '05.

68	M.H. 169/05	F	60	Spheroidal cell carcinoma of left breast.	Supra-clavicular glands, humerus, frontal bone, vertebrae, perosteum of tibia.	... ..	(i) Much emaciated.	(i) 22 Aug. '05. (ii) 26 Oct. '05.
69	C.V. 167/05	F	64	Spheroidal cell carcinoma of left breast.	Liver, pericardium, lung, axillary and cervical glands.	... ..	(i) Long mesoecum. (ii) Very fat.	(i) 11 Aug. '05. (ii) 25 Oct. '05.
70	C.A. 145/05	F	68	Spheroidal cell carcinoma of right breast.	Right and left axillary glands, humeral glands, adrenal.	... ..	(i) Meckel's diverticulum.	(i) 3 Nov. '04. (ii) 30 Aug. '05.
71	H.N. 123/05	F	68	Spheroidal cell carcinoma of left breast.	*Axillary glands, liver.	Left pleural effusion. Gallstone. Uterine fibroids.	(ii) Well nourished.	(i) 3 March '05. (ii) 26 June '05. (iii) Amputation of breast Sept. '03.
72	E.M. 49/05	F	71	Spheroidal cell carcinoma of left breast.	Liver, *axillary and pre-auricular glands.	Old pulmonary tuberculosis. Gallstones; fistula between gall-bladder and transverse colon. Chronic interstitial nephritis.	(ii) Emaciated.	(i) 18 July '04. (ii) 20 March '05.
73	C.B. 147/05	F	73	Spheroidal cell carcinoma of left breast.	Bronchial gland.	Chronic interstitial nephritis.	(ii) Well nourished.	(i) 1 May '02. (ii) 11 Sept. '05.
74	P.L.L. 176/05	F	80	Spheroidal cell carcinoma of right breast.	Right and left axillary glands, lung, peritoneum, diaphragm.*	Fibro-adenoma of ovary.	(ii) Much emaciation.	(i) 15 July '05. (ii) 1 Nov. '05.
75	M.T. 124/05	F	90?	Spheroidal cell carcinoma of right breast.	Axillary glands,* right pleura.	Extreme fatty degeneration of vertebrae. Thyroid cyst. Fatty heart. Extreme atheroma of vessels. Liver very fatty. Two pedunculated lipomata in caecum.	(i) Left lobe of liver rudimentary. (ii) Well nourished.	(i) 19 Dec. '04. (ii) 27 June '05.

TABLE III.—SYNOPSIS OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnor- malities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
76	M.A.H. 83/05	F	25	Proliferating cystadenoma of ovaries.	Liver, lymphatic glands.	(General peritonitis. Double hydronephrosis.	(ii) Very emaciated.	(i) 28 April '05. (ii) 4 May '05. (iii) Ovariectomy '04.
77	M.C. 185/05	F	44	Papilliferous cystadenoma of right kidney.	Lung, pleura, liver, bronchial, cervical and abdominal glands, adrenal.	... ..	(ii) Emaciation. Hosp. p.m. 150.	(i) 10 Nov. '05. (ii) 16 Nov. '05. (iii) Laparotomy 15 Nov. '05.
78	E.M. 73/05	F	49	Papilliferous cystadenoma of ovary.	Uterus, liver, thoracic duct, pel- vic, lumbar, celiac and mesenteric glands.	General peritonitis with purulent ascites.	(ii) Emaciation. Hosp. p.m. 77.	(i) 7 April '05. (ii) 17 April '05. (iii) Laparotomy Feb. '04.

## SARCOMATA.

No	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnor- malities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
1	W.L. 17/05	M	63	Mixed cell sarcoma of lung.	Liver, bronchial and mediastinal glands, rib, right abdominal.	Old rickets.	(ii) Great emacia- tion.	(i) 10 Oct. '04. (ii) 30 Jan. '05.
2	E.A. 193/05	F	26	Small round cell sarcoma of right ovary.	Left ovary, adrenal, heart.	Ascites.	(ii) Well nourished. Hosp. p.m. 151.	(i) 27 Oct. '05. (ii) 22 Nov. '05.

3	E.P. 56/05	M	27	Round cell sarcoma of left kidney.	Lungs, lymphatic glands, liver.	Edema of legs.	(i) Slight emaciation. Hosp. p.m. 62.	(i) 24 Feb. '05. (ii) 1 April '05.
4	E.P. 314/05	F	28	Small round cell sarcoma of right femur.	Left femur, ossa innominata, left tibia.	Renal calculus, left kidney (uric acid).	(ii) Extreme emaciation.	(i) 8 Aug. '01. (ii) 27 July '05. (iii) Amputation right thigh.
5	G.C. 61/05	M	34	Small round cell sarcoma of scapula.	Liver, lumbar and temporal glands, gall-bladder, pleurae, dura-mater.	... ..	(ii) Well nourished.	(i) 28 March '05. (ii) 10 April '05.
6	M.J. 112/05	F	41	Small round cell sarcoma of pylorus.	Glands in gastro-hepatic omentum and above pancreas	... ..	(ii) Much emaciation. Hosp. p.m. 106.	(i) 1 June '05. (ii) 9 June '05. (iii) Gastro-jejunos-tony.
7	G.W.B. 142/05	M	43	Small round cell sarcoma of testicle.	Pelvic, iliac, and lumbar glands.	Right hydronephrosis.	(ii) Much emaciation.	(i) 21 July '05. (ii) 24 Aug. '05.
8	H.W. 178/05	F	55	Small round cell sarcoma of small intestine.	None.	Adherent pericardium. Perforation; peritonitis old and recent. Stereocoral ulceration.	(ii) Much emaciation. Hosp. p.m. 142.	(i) 21 Sept. '05. (ii) 27 Oct. '05.
9	M.W. 103/05	F	82	Small round cell sarcoma of uterus.	Liver, iliac glands.	Double hydronephrosis, gall-stones.	(ii) Body thin.	(i) 4 May '05. (ii) 4 June '05.
10	R.F.C. 62/05	M	46	Spindle cell sarcoma of caecum.	Liver, caeliac and mesenteric glands.	Intestinal perforation. Purulent peritonitis.	(ii) Emaciated. Hosp. p.m. 70.	(i) 9 Feb. '05. (ii) 10 April '05.
11	A.C. 152/05	F	67	Spindle cell sarcoma of bladder.	None.	Right hydronephrosis.	(ii) Thin.	(i) 20 March '01. (ii) 22 Sept. '05. (iii) Exploration of bladder '03. Supra-pubic cystotomy June '04.



TABLE III.—SYNOPSIS OF POST-MORTEM CASES—*cont.*

No.	Initials and Cancer Register Number.	Sex.	Age at Death.	Nature of new growth and part primarily affected.	Sites of Secondary new growth.	Other morbid changes present.	(i.) Congenital abnor- malities. (ii.) General remarks.	(i.) Date of admission. (ii.) Date of death. (iii.) Surgical operation, if any.
12	B.R. 116/05	M	22	Myeloid sarcoma of right humerus.	Pancreas, skin, lung, bladder, kid- ney, intestine, heart, lymphatic glands.	... ..	(i) Much emacia- tion. (ii) Hosp. p.m. 112.	(i) 14 Feb. '05. (ii) 14 June '05.
13	A.M.S. 186/05	F	34	Melanotic sarcoma of skin of heel.	Skin, breast, thy- roid, liver, brain, lung, kidney, skull, most glands.	... ..	(ii) Great emacia- tion.	(i) 30 Oct. '05. (ii) 17 Nov. '05.
14	H.C. 89/05	F	55	Melanotic sarcoma of left orbit.	Liver, uterus.	Old pulmonary tuberculosis.	(ii) Some emacia- tion.	(i) 8 Dec. '04. (ii) 16 May '05.
15	M.A.P. 195/05	F	64	Melanotic sarcoma of skin of left thumb.	Liver, subcutane- ous tissue, axillary and retroperitoneal glands.	Adenoma of thyroid	(ii) Emaciated.	(i) 15 Sept. '05. (ii) 3 Dec. '05.
16	W.F. 192/05	M	25	Lymphosarcoma of mediastinum.	Heart, pericar- dium, mediastinal and cervical glands	... ..	(ii) Slight emacia- tion. Hosp. p.m. 153.	(i) 5 Oct. '05. (ii) 22 Nov. '05.
17	M.B. 198/05	F	39	Peri-entelioma of right breast.	Lung, liver, ovary, skin.	... ..	(ii) Much emacia- tion.	(i) 28 Oct. '05. (ii) 5 Dec. '05.
18	W.R. 1/05	M	42	Endothelioma of liver.	Liver, left biceps, humbar, celiac and bronchial glands.	Ascites.	(ii) Hosp. p.m. 3.	(i) 30 Dec. '04. (ii) 1 Jan. '05.
19	C.D. 120/05	F	45	Endothelioma of cer- vix uteri.	Uterus, liver, humbar glands.	Right hydronephrosis.	(ii) Much emacia- tion.	(i) 20 March '05. (ii) 23 June '05.

20	M.P. 85/05	F	47	Endothelioma of right breast.	Liver.	Thyroid adenoma. Pleural effusion right side. Left lung, recent vomica.	(i) Patent foramen ovale. (ii) Great emaciation.	(i) 1 May '05. (ii) 14 May '05.
21	E.F. 128/05	F	48	Endothelioma of omentum.	Liver.	...	(ii) Well nourished.	(i) 26 Sept. '04. (ii) 11 July '05.
22	D.R. 34/05	M	48	Endothelioma of tongue.	None.	Casuous mass in upper lobe of left lung. Miliary tuberculosis of both lungs. Peritoneal adhesions around stomach.	(ii) Considerable emaciation.	(i) 15 Nov. '04. (ii) 25 Feb. '05.
23	G.S.B. 64/05	M	48	Endothelioma of mesophagus perforating trachea and right pleura.	None.	Right pyopneumothorax.	(i) Hosp. p.m. 71.	(i) 8 April '05. (ii) 10 April '05.
24	S.J. 215/05	F	56	Perithelioma of right breast.	Brain.	...	(ii) Well nourished.	(i) 6 Dec. '05. (ii) 29 Dec. '05.
25	J.J. 115/05	M	56	Perithelioma of retroperitoneal glands.	Lymphatic glands, bladder, heart, liver, adrenal, intestine, kidney, vena cava, skin.	...	(ii) Much emaciation. Hosp. p.m. 111.	(i) 31 Jan. '05. (ii) 14 June '05.

# ON GAMETOID TYPES OF MITOSIS IN THE SO-CALLED "GONORRHŒAL WART."

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## INTRODUCTION.

IN 1903 Messrs. Farmer, Moore, and Walker drew attention to certain resemblances between the cells of malignant new growths and those of gametic tissues.

These observations they have since extended, and briefly their latest conclusions are as follows:—

1. The forms of mitosis known as *heterotype* (reducing division) and *homotype* (post-heterotype division), which are normally seen during the evolution of the spermatozoön and the maturation of the ovum, are also found in the dividing cells of the malignant new growths.

2. The so-called "*Plimmer Bodies*" frequently present in the cytoplasm of the malignant cell are, in fact identical with the *archoplasmic vesicles* normally found in the cytoplasm of the spermatogenetic cells.

3. Since the cells of innocent neoplasms and inflammatory masses of tissue never exhibit these peculiar types of mitosis, they may therefore, when found, be looked upon as a *certain sign of malignancy*.

In 1904 I published the results of an investigation into the nuclear changes characterising the cells of papilliferous ovarian cysts.\* My reason for choosing these neoplasms was that "in them is met every grade of epithelial activity between frank innocence and undoubted malignancy."

It was shown that the epithelial cells constituting the bulk of these tumours frequently exhibit a type of nuclear

\* "The Cytology of Papilliferous Ovarian Cysts." Archives of the Middlesex Hospital, vol. iii. p. 178.

division similar to the heterotype and homotype mitosis as well as that *multipolar nuclear division* which is a striking feature of malignant growths.

It follows, therefore, that these types of mitosis are not alone associated with growths exhibiting the complete picture of malignancy, but also with semi-malignant tumours, which, while showing no tendency to metastasis by the blood or lymph streams, are yet capable of a secondary local implantation closely resembling certain processes admittedly due to infective agents.

Seeing, then, that similar types of cell division certainly occur in two groups of new growths which differ in several respects yet agree in one important particular, I have investigated the types of nuclear division met with in a group which at first sight differs much from the semi-malignant new growths, but agrees with them in respect of its extraordinary power of secondary local implantation, namely, the so-called "gonorrhœal wart."

These growths, in spite of their name, have almost certainly no necessary association with gonorrhœa. There are, in fact, very strong reasons for regarding them as due to some specific "wart infection" *sui generis*. They are frequently seen in the absence of gonorrhœa, and at times are primary in situations where the gonococcus is not found, such as the umbilicus, between the toes, etc. Moreover, their structure is not inflammatory, but resembles that of the true neoplasms in exhibiting a more or less perfect reproduction of the tissues from which they grow. Leucocytal exudation, massive accumulation of one type of cell to the exclusion of all others, bizarre and unnatural arrangement of the cells constituting them, and local grouping of these effects around some central focus are all absent. In short, microscopically they no more deserve the term "inflammatory" than the intracystic papilloma of the ovary.

At a laboratory meeting of the Pathological Society of London, held on May 2nd, 1905, I showed preparations obtained from these growths exhibiting types of cell division similar to the heterotype and homotype mitosis found in gametic tissues. The present paper is a continuation of these early observations, and confirms them in all respects.

## METHODS.

The material investigated comprises twenty specimens of "gonorrhœal" warts obtained from different patients, male and female. The fixatives employed were chiefly acetic-alcohol, Hermann's solution, and Flemming's stronger solution. Embedding in paraffin was carried out by the rapid method. The blocks have been cut serially in order to avoid the fallacy arising from interpreting the number and arrangement of the chromosomes from a portion of a cell instead of from the entire one. In most cases the sections were  $5\mu$  in thickness, and were stained by various methods, including Flemming's stain and Heidenhain's Iron Hæmatoxylin stain, but especially by an original process already described.\* The slides thus prepared were examined under a magnification of from 450 to 1,350 diameters obtained by a Zeiss  $\frac{1}{12}$  apochromatic objective N.A. 1.3, and compensating oculars 4, 8, and 12. I have found the Nernst electric light the best suited for this work because it presents a single band of pure white light, admirably adapted for focussing by the condenser on the object. Monochromatic light has been obtained by the use of a Gifford's screen or a dark blue glass.

The drawings shown on plates I and II have been made with the camera lucida.† It must be remembered that mitoses occupy a certain thickness of the section, and that under the high magnification used all the parts of the mitotic figure are never in focus at one time. The drawings, therefore, represent on one plane all the chromosomes of each cell. In all the examples drawn the entire cell has been contained within the thickness of a single section.

## THE CYTOLOGY OF "GONORRHŒAL WARTS."

## The Chromosome Content.

This has been arrived at by counting the number of chromosomes in each cell of a consecutive hundred clearly

\* Bonney, "Archives of the Middlesex Hospital," vol. vi. p. 89, and "Lancet," Jan. 27, 1906.

† It may be worth mentioning that I have found that drawing with the camera lucida is greatly facilitated by covering the tip of the pencil with gold leaf.



defined dividing cells taken from several cases. The results are as follows :—

Number of chromosomes .	6	7	8	9	10	11	12
Number of cells . . .	2	2	2	2	11	3	13
Number of chromosomes .	13	14	15	16	17	18	19
Number of cells . . .	4	7	5	26	2	4	0
Number of chromosomes .	20	21	22	23	24	25	26
Number of cells . . .	2	0	0	0	3	2	2
Number of chromosomes .		27	28	29	30	31	32
Number of cells . . .		1	1	0	4	0	2

It therefore appears from these figures that 75 % at least of the epithelial cells which constitute the bulk of these growths exhibit a reduction in the number of chromosomes to somewhere about half that usually held to be the normal somatic number for man, namely 32.

That in many cases the number of chromosomes observed in a single cell falls short of 32 and 16 respectively is explained by the difficulty of accurately counting them.

#### The Types of Mitosis Observed.

The prevailing type of mitosis is the *homotype*, but there are seen as well a moderate proportion of *heterotype divisions* and a smaller number exhibiting the *somatic* formation. The figures to which the descriptions below refer are found on Plates I and II. For the photo-micrographs, reproduced on Plate II, I am indebted to my friend, Mr. F. Shillington Scales.

#### Somatic Division.

The somatic prophase appears very sparsely in its earliest form, but occasional examples are met with. The same may be said to apply to the later stages of this phase, but Fig. 1 illustrates a good specimen in which the delicate V-shaped chromosomes are already formed preparatory to arranging themselves on the achromatic spindle. The slightly beaded extremities of the chromosomes are well seen.

The metaphase is commoner. Figs. 2 and 3 are drawn from examples observed in polar view and profile respectively. The beaded appearance of the extremities of the chromosomes has disappeared.

Telophase and anaphase appearances are common, but owing to the close crowding of the chromosomes it is often difficult or impossible to determine whether they arise from somatic, heterotype, or homotype divisions.

#### Heterotype Division.

Good examples of the early heterotype prophase are not uncommon.

Fig. 4 shows well the loosely-coiled and beaded spirème. Fig. 5 illustrates an example of the *synaptic figure* described by Moore, whilst Fig. 6 shows the typical skein-like arrangement of the chromatic thread which is characteristic of a certain stage in the heterotype prophase. A photograph of this cell is seen on Plate II., Fig. 16.

Examples of heterotype metaphase are illustrated in Fig. 7 and in Plate II., Fig. 17. The ovate, slightly pointed chromosomes lying in the longitudinal axis of the spindle are very obvious, and should be compared with Fig. 8, which is drawn from a good example of this phase occurring in a preparation of normal human testis. Polar views of this phase are also seen presenting a characteristic circular figure, with irregular excrescences.

#### Homotype Division.

As has been stated the large majority of the mitoses observed belong to this group. A phase very plentifully observed is the *post-heterotype prophase*, of which Figs. 9 to 11, and 18, illustrate the chief appearances.

Foremost to be noted is the thick, short, and slightly curved shape of the chromosomes, many of them exhibiting a longitudinal line of cleavage. They are grouped together in the centre of the nucleus, the nuclear membrane generally being intact. Spindle rays are usually visible, but are ill-formed and indistinct. The chromosomes appear to lie upon them in most instances.

In Fig. 12 the nuclear membrane has almost disappeared and the chromosomes have lengthened out somewhat, and are splitting longitudinally in the line of cleavage already referred to. This characteristic of the post-heterotype prophase has been emphasised by Farmer. A definite centrosome is here

observable, which is not the case in Figs. 9 to 11, which represent an earlier stage.

Fig. 13 illustrates another form of homotype prophase, which should be compared carefully with Fig. 1. These two cells lay in close proximity, so that their characteristics could be easily contrasted. The thicker, larger, and non-beaded chromosomes in Fig. 13 present a striking difference from the more delicate beaded variety seen in the somatic cell (Fig. 1), while the number of chromosomes is exactly half that found in Fig. 1.

Fig. 13 should also be compared with Figs. 9 to 11. These illustrate the first homotype or post-heterotype prophase, and it will at once be noticed that although they agree with Fig. 13 in possessing the reduced chromosome content, yet there is a great difference in the shape of the individual chromosomes.

I think that there can be little doubt but that the homotype mitosis is not limited as in mammalian gametic cells to a single division, but occurs repeatedly. This is in accordance with the observations made by Farmer, Moore, and Walker in malignant new growths, and with my own experience in the papilliferous ovarian cysts. Fig. 13 probably illustrates one of these later homotype divisions. The interesting analogy in this connection between malignant new growths and prothallial tissue in the lower plants has been remarked by Professor Farmer.

Fig. 14 illustrates the beginning of the homotype metaphase; Fig. 15 shows a polar view of a rather later stage.

#### **Cell Division in the Connective Tissue Elements of Gonorrhoeal Warts.**

In the large number of sections I have examined no mitoses were observable in the connective tissue elements of these growths. Probably these cells divide by amitosis.

#### **The Sites of Divisional Types.**

No particular localities in these growths have been recognised at which it might be said that one type of mitosis was alone characteristic. The best examples of heterotype

division were present in the very edge of the growth but were not strictly limited to it.

Somatic divisions were chiefly found in the cells of the rete Malpighii, whilst the large post-heterotype prophase was oftenest seen in the prickle-cell layer. Nevertheless no definite order could be made out, the various types of cell division often lying in close proximity.

#### **The Absence of Multipolar Mitosis.**

An important point of difference between the gonorrhoeal warts and malignant and semi-malignant growths lies in the complete absence in the former of the characteristic multipolar mitosis.

This statement is based on the examination of over 2,000 sections.

#### **The Absence of "Plimmer Bodies," or "Archoplasmic Vesicles."**

I have also been unable to find in the cells of these new growths any evidence of the so-called "Plimmer Bodies," lately described by Farmer, Walker, and Moore as archoplasmic vesicles.

#### **Conclusions.**

It is evident that the statement that a gametoid type of mitosis is peculiar to the cells of malignant new growths, cannot be accepted without qualification, since it is also present in the cells of the semi-malignant intracystic papilloma of the ovary, and of the "gonorrhoeal wart."

There is, however, one feature common to the cells of them all, namely their power of secondary local implantation.

In my previous paper \* I suggested that these forms of cell division were probably symptomatic of a condition of independent existence on the part of the cell rather than a causative factor in the production of the neoplasm. The present work supports this view.

\* "Cytology of Papilliferous Ovarian Cysts." Archives of the Middlesex Hospital, vol. iii. p. 178.



Fig. 12.

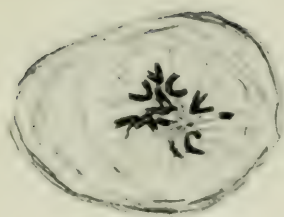


Fig. 7.



Fig. 1.

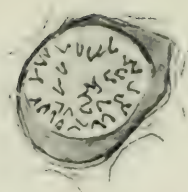


Fig. 15.



Fig. 8.



Fig. 2.

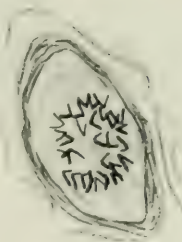


Fig. 13.

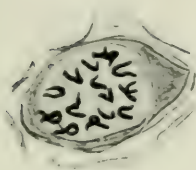


Fig. 9.



Fig. 3.

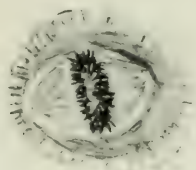


Fig. 14.



Fig. 10.

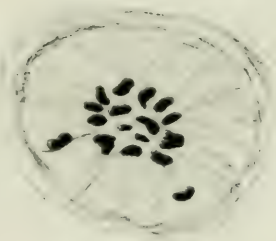


Fig. 4.

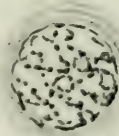


Fig. 5.

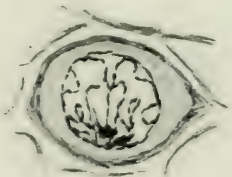


Fig. 6.

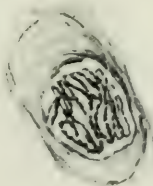
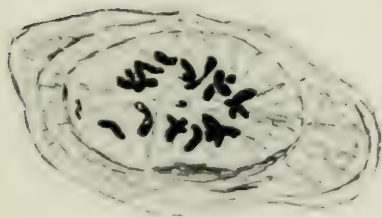


Fig. 11.







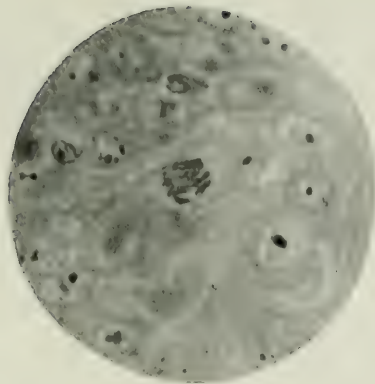


Fig. 16.

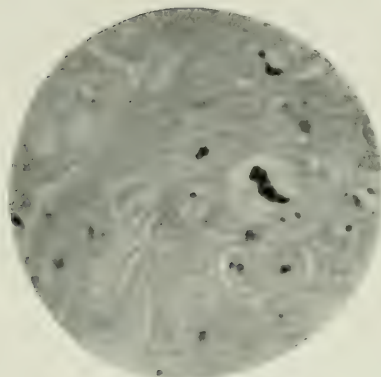


Fig. 17.



Fig. 18.



## THE PRECIPITIN REACTION AND MALIGNANT NEW GROWTHS.

(Experiments in which the juice expressed from new growths was used for preparing the antisera.)

BY W. S. LAZARUS-BARLOW, M.D., F.R.C.P.

DURING the past few years observations have been accumulating to show that the animal body possesses the power of producing within itself specific substances as the result of inoculation. Starting from this standpoint attention has been paid during the past two years in the Cancer Laboratory of the Middlesex Hospital to the class of precipitins, with the object of determining whether it is possible to obtain some diagnostic method for cancer, particularly in its earlier stages. Other aspects of this same question are considered elsewhere in the present as well as in the last volume of the Cancer Reports.

In the present paper the general methods employed in the research only call for remark upon points in which they differ from those used by other workers in this laboratory. Shortly, they only depend upon the difference in the nature of the material used in this research for inoculation. Whereas Dr. Douglas employed natural fluids from cancerous patients, and Dr. Colwell employed alkali-albumins derived from cancerous patients, I used as the material for inoculation the expressed juice of the malignant growths themselves.

As a rule the growths which were subjected to pressure were derived from the dead body, since it was impossible to obtain a sufficient amount of cancerous material from a single operation case for obvious reasons. In most instances the material used for expression was not that constituting the primary growth, partly because this was often undergoing necrosis and putrefaction, and partly because in those cases

in which the primary growth was not undergoing retrogressive changes it was so largely composed of fibrous tissue as to yield hardly any juice, even on considerable and prolonged pressure.

The expressed juice, to which was added enough .8 per cent. saline solution to ensure a ready flow through the needle of the syringe, consisted almost entirely of cells as determined by the microscope. Its preservation was a matter of difficulty and importance in view of the fact that the animal was to receive repeated injections. At first chloroform was added in small quantities, but this method was soon found to have two grave objections. Firstly, juices to which it was added showed a great tendency to separate into a stringy solid portion, which could only be broken up with difficulty, so that the needle of the syringe easily became blocked, and the danger of bacterial contamination was enormously increased. And secondly, the chloroform separated out from the fluid part of the juice and attached itself so firmly to the solid portion that it was impossible to drive it off by a gentle heat. From the latter cause a certain number of the earlier animals died when an attempt was being made to increase the doses of injected material with some rapidity. Preservation without any addition, simply by keeping the material in an ice chamber, was tried, but proved useless owing to the fact that the material was not aseptic in the first instance, and could not be rendered so without altering its composition to an extent that would have rendered it useless for the purpose in hand. It was consequently decided to add sufficient chinisol to bring the entire volume of juice to a 1-2000 strength of that substance, and to keep the flasks of juice in the cold chamber between the times of injection. Intra-peritoneal and subcutaneous injections of a 1-2000 solution of chinisol into rabbits had shown that this strength is harmless.

The juices employed in the research were derived from the following cases:—(1) Columnar cell carcinoma of the gall-bladder (large hepatic extension from the primary mass), (2) spheroidal cell carcinoma of the stomach (primary growth), (3) melanotic sarcoma, (4) spheroidal cell carcinoma of the breast (hepatic metastases, two cases), (5) squamous cell



carcinoma of the vagina (large extension of primary mass), (6) squamous cell carcinoma of cervix uteri (hepatic metastases), (7) squamous cell carcinoma of tonsil (glandular metastases), (8) papilliferous cystadenoma of ovary (primary mass). The diagnosis was made microscopically in each case.

Immunisation by intra-peritoneal, by subcutaneous, and by intravenous injections were tried, but finally the two latter were discarded for intra-peritoneal injection. Rabbits were used, and the animals were killed by rapid bleeding. The number of injections varied, and exact details on this point will be given in connection with each experiment described later. Speaking generally, the earlier series of experiments, in which chloroform was used as a preservative for the juice, comprised a smaller number of injections, and a smaller total amount of juice was injected. The reason of this was the severe collapse induced in the animals by intra-peritoneal injection of even a relatively small amount of fluid.

In all cases the post-mortem examination of the animals, after they had been bled for the purpose of obtaining their serum, showed that changes had taken place locally in the peritoneal cavity. In the most successful cases these changes only consisted in the localisation of the solid portions of the fluid injected as a putty-like mass, and the formation of a small amount of inflammatory material around them. In no case was the abdominal cavity completely free from local accumulations of the solid portions of the injected cancerous material, but in the later experiments the amount of secondary inflammatory material was insignificant. In the earliest experiments a very large amount of inflammatory material was present in cases that had been injected a sufficient number of times to make their serum valuable, and at the very commencement of the research a great number of animals died as the result of the first or of the second injection. This is in great contrast to our experience in injecting fluids such as blood, pleural and ascitic fluid, which are borne by the animals perfectly well, even though derived from the same post-mortem cases as the cancer material used for the purpose of the present research.

### **I.—The Effect of Heat on the Serum and Antiserum, and the Source of the Precipitate.**

The effect of heating the two factors that enter into the precipitin reaction, or one of them, may be considered along with the question of the source of the precipitate itself.

To determine these questions the effect of heat alone was first considered. Small tubes of antiserum were immersed in a bath of water and kept at a constant temperature for half an hour. The temperatures chosen were 55° C., 60° C., 65° C., 66° C., 67° C., 68° C., 69° C., 70° C. The result was not the same in all cases, for whereas a "uterus" antiserum showed commencing coagulation at 68–69° C., and complete coagulation at 70° C., a "breast" antiserum showed complete coagulation at 67° C. Further, it was noted that the tubes that had been exposed to still lower temperatures, although their contents might be fluid, frequently showed a turbidity that rendered them useless for delicate precipitin reactions. There is no doubt that the turbidity was evidence of either a commencing coagulation or was a precursor of coagulation. Ultimately, it was found that exposure of the serum or the antiserum to a temperature of 56° C. for half an hour was the furthest limit to which heating could be carried without introducing alterations in the albuminous fluids that entirely vitiated the experiment.

In each of the three following experiments four tubes were prepared. The resulting precipitum was allowed to settle, and after twenty-four hours was collected into calibrated thermometer tubes according to the method recommended by Nuttall. When the precipitum had settled in these, i.e. twenty-four hours later, the volume of the precipitate was read off.

The antisera used were as follows:—

EXPERIMENT I.—An antiserum obtained by injecting a rabbit with the juice expressed from a mass of glands secondarily affected from a squamous cell carcinoma of the tonsils. The quantities injected and the number of days between successive injections were—

5—8—10 cc. injected.

4—4—2 days between injections.

EXPERIMENT II.—An antiserum derived from a rabbit after injecting the juice expressed from a mass of peritoneal growth extending from a papilliferous cystadenoma of the ovary. The quantities injected and the days between successive injections were—

10—10—10—10 cc. injected.

6—3—4—2 days between injections.

EXPERIMENT III.—An antiserum obtained by injecting the juice expressed from the hepatic metastases in a case of squamous cell carcinoma of the cervix uteri. The quantities injected and the number of days between the successive injections were—

5—8—10—10 cc. injected.

2—5—10—3 days between injections.

In all instances the word "heated" (below) signifies that the serum or antiserum was kept at a temperature of 56° C. in a waterbath for half an hour. In each experiment .5 cc. of the antiserum was added to .5 cc. of a 1-100 dilution of normal human blood serum, the fluids were well mixed, allowed to stand for twenty-four hours, and the volume of the precipitate calculated after a further period of twenty-four hours.

#### EXPERIMENT I.

	Volume of Precipitate.
Antiserum (heated) + dilute human serum (unheated) . . .	.0064 cc.
" (unheated) + " " " (heated) . . .	.0080 cc.
" (heated) + " " " (heated) . . .	.0056 cc.
" (unheated) + " " " (unheated) . . .	.0096 cc.

#### EXPERIMENT II.

Antiserum (heated) + dilute human serum (unheated) . . .	.0024 cc.
" (unheated) + " " " (heated) . . .	.0072 cc.
" (heated) + " " " (heated) . . .	.0016 cc.
" (unheated) + " " " (unheated) . . .	.0080 cc.

#### EXPERIMENT III.

Antiserum (heated) + dilute human serum (unheated) . . .	.0056 cc.
" (unheated) + " " " (heated) . . .	.0120 cc.
" (heated) + " " " (heated) . . .	.0064 cc.
" (unheated) + " " " (unheated) . . .	.0144 cc.

The results in the three experiments are entirely concordant, and show that the maximum precipitum is given when the serum and antiserum are unheated, and that the minimum precipitum is given when both serum and antiserum were heated. When only one of the two fluids is heated the amount of precipitum is intermediate between the two extremes.

With regard to the source of the precipitum it is clear from the above that both serum and antiserum enter into its composition, and from the experiments quoted it appears that heating of the serum portion produces a smaller diminution than heating of the antiserum. It must be remembered, however, that the actual amount of proteid in the .5 cc. of the serum factor was far less than the amount of proteid in the .5 cc. of the antiserum factor owing to the 1-100 dilution to which the serum had been subjected before mixing with the antiserum—which was undiluted.

The question as to the source of the precipitum was considered from another point of view. Experiments were carried out in which, on the one hand, constant amounts of antiserum were mixed with increasing quantities of serum, and, on the other hand, constant quantities of serum were mixed with increasing quantities of antiserum. Below are given two such experiments.

#### EXPERIMENT IV.

							Volume of Precipitate.
100 cmm. of antiserum + 1,000 cmm. of .5 % normal human serum .							.018 cc.
"	"	"	"	1 %	"	"	.022 cc.
"	"	"	"	2 %	"	"	.028 cc.
"	"	"	"	3 %	"	"	.029 cc.
"	"	"	"	4 %	"	"	.0287 cc.
"	"	"	"	5 %	"	"	.024 cc.

The antiserum used in this case was derived from a rabbit that had been injected with the juice expressed from a mass of pleural metastases in a case of melanotic sarcoma. The quantities injected and the number of days between successive injections were—

2—5—5—5 cc. used for injection.

4—3—5—6 days between injections.



## EXPERIMENT V.

							Volume of Precipitate.
0.5 cc. antiserum +	0.5 cc. of	1-100 dilution of	normal human serum.	.	.	.	0.016 cc.
10 cc.	"	"	"	"	"	"	0.024 cc.
15 cc.	"	"	"	"	"	"	0.040 cc.
20 cc.	"	"	"	"	"	"	0.048 cc.
25 cc.	"	"	"	"	"	"	0.056 cc.
30 cc.	"	"	"	"	"	"	0.072 cc.
40 cc.	"	"	"	"	"	"	0.104 cc.
50 cc.	"	"	"	"	"	"	0.135 cc.

The antiserum used in this case was one obtained by injecting a rabbit that had been injected with cancerous growth from the tonsil, and was the same as used in Experiment I.

There is reason, however, to believe that the serum itself does not form so large a proportion of the precipitum as the antiserum. For if the same serum and antiserum are used for comparative experiments it appears that increase in the amount of antiserum produces a disproportionately greater increase in the resulting precipitum than increase in the amount of serum. The following experiment is a continuation of Experiment V., and should be compared with it.

## EXPERIMENT VI.

1 cc. antiserum +	0.5 cc. of	1-200 dilution of	normal human serum	.	.	.	0.0024
"	"	"	1-100	"	"	"	0.0024
"	"	"	2-100	"	"	"	0.0024
"	"	"	3-100	"	"	"	0.016
"	"	"	4-100	"	"	"	0.0024
"	"	"	5-100	"	"	"	0.0032

Considering the small volumes of precipitate in this experiment by themselves and the margin of error, it might almost be held that the serum itself does not enter into the composition of the precipitum at all; but Experiment IV., which deals with precipitates ten times as great, is so conclusive and is so typical of a large number of observations that there can be no doubt that the precipitate is partly formed at the expense of the serum.

The experiments given above permit of the following conclusions:—

1. The precipitum is formed at the expense of both the antiserum and the serum, but by far the greater part is formed at the expense of the antiserum.



2. Exposure of either the serum or the antiserum to a temperature of  $56^{\circ}$  C. for half an hour immediately before mixing the fluids diminishes the amount of the resulting precipitum. Temperatures higher than  $56^{\circ}$  C. cause changes in the fluids (opalescence), which interfere with experiments to determine whether the precipitin reaction is entirely abolished at temperatures higher than  $56^{\circ}$  C. but lower than those at which actual coagulation of the serum or antiserum takes place.

## II.—The Effect of Desiccation of the Antiserum.

Desiccation of the antiserum appears to be without effect upon the quantity of precipitum. This point is shown in the two following experiments:—

### EXPERIMENTS VII. AND VIII.

						Precipitate
100 cmm. of "melanotic" antiserum	+	1 cc. of .5 % dilution of serum A				.0103 cc.
" " " " (dried)	"	" " "	"	"	"	.0103 cc.
100 cmm. of "melanotic" antiserum	+	1 cc. of .5 % dilution of serum B				.0111 cc.
" " " " (dried)	"	" " "	"	"	"	.0111 cc.

In each instance the antiserum was first measured out into a watch glass, and then dried at a temperature of  $37^{\circ}$  C. over a water-bath. It was then re-dissolved in water and made up to the original volume. The experiment not only shows that desiccation is without effect upon the volume of the resulting precipitum, but incidentally shows that the serum itself takes a share in the formation of the precipitum. For the volumes of the precipitum are different in the two experiments, and different, though perfectly normal, human sera were used in the two cases. The same point has been shown by Dr. Douglas in greater detail elsewhere.

## III.—The Degree of Specificity of the Antiserum.

Considering the high degree of specificity that obtains in the case of antisera produced by inoculation with different varieties of bacteria, and the possibly greater degree of specificity manifested in the precipitin and hæmolysin reactions brought about by injecting blood and other fluids of one species of animal into another species, it was thought possible that a similarly high degree of specificity might be manifested by the sera of animals that had been subjected to

injections of different varieties of new growth. That the antisera so produced would show a common "anti-human" precipitin reaction, since all the material used for injection was derived from human sources, was anticipated. But considering the extreme delicacy of the reaction it was hoped that it would be possible to differentiate sarcomata from carcinomata by its aid, if not to differentiate the varieties of the two great malignant groups among themselves. As will be seen later, these hopes were not fulfilled, and the only specificity that manifested itself was that which depended upon the common human character of the material used for injection. In the case of all the rabbits that had been subjected to a sufficiently long treatment the rabbit serum produced a precipitate when mixed with human serum, or with any other albuminous material derived from human sources; but no difference was observed whether the serum or other albuminous fluid was derived from a cancerous or a non-cancerous patient or from a healthy individual.

The matter is equally inconclusive from still another point of view. When using different strains of the same variety of bacillus (e.g. *B. typhosus*) it is found that in respect of the agglutination reaction the greatest degrees of agglutination are obtained when the antiserum is tested against the same strain of bacilli as was used in immunising the animal. On these grounds it might be expected that the maximum precipitum would be produced when the serum of one of the animals used in the present research was mixed with some of the fluid which was used to inoculate the animal. This is by no means the case, and of a variety of fluids used for injecting the different animals it was quite uncertain which would give the greatest precipitum with a given antiserum. The experiments which form the basis of the preceding remarks have been repeated a number of times with the same results. The following experiment is a representative one:—

## EXPERIMENT IX.

	Vol. of Precipitate.
.5 cc. "uterus" antiserum + .5 cc. of 1-100 normal human serum.	.0072 cc.
" " " " " original uterus fluid	.0072 cc.
" " " " " original tonsil fluid.	.0032 cc.
" " " " " original ovary fluid	.0040 cc.

					Vol. of Precipitate.
5 cc. "uterus" antiserum +	5 cc. of 1-100	original breast fluid	.	.	'0080 cc.
" "	" "	normal rabbit serum	.	.	'0064 cc.
" "ovary" antiserum	" "	normal human serum	.	.	'0080 cc.
" "	" "	original uterus fluid	.	.	'0176 cc.
" "	" "	original tonsil fluid.	.	.	'0056 cc.
" "	" "	original ovary fluid.	.	.	'0056 cc.
" "	" "	original breast fluid	.	.	'0056 cc.
" "	" "	normal rabbit serum	.	.	'0040 cc.
" "tonsil" antiserum	" "	normal human serum	.	.	'0232 cc.
" "	" "	original uterus fluid	.	.	'0160 cc.
" "	" "	original tonsil fluid.	.	.	'0088 cc.
" "	" "	original ovary fluid	.	.	'0080 cc.
" "	" "	original breast fluid	.	.	'0072 cc.
" "	" "	normal rabbit serum	.	.	trace.
" "breast" antiserum*	" "	normal human serum	.	.	'0072 cc.
" "	" "	original uterus fluid	.	.	'0064 cc.
" "	" "	original tonsil fluid.	.	.	'0032 cc.
" "	" "	original ovary fluid	.	.	'0032 cc.
" "	" "	normal rabbit serum	.	.	trace.

Placing the results obtained in this series of experiments in the order of magnitude of the precipita in each series, it is seen that no support is given to the hypothesis of a particular specificity of the antiserum.

*"Uterus" antiserum :*

Original breast fluid.  
 { Normal human serum.  
 { Original uterus fluid.  
 Normal rabbit serum.  
 Original ovary fluid.  
 Original tonsil fluid.

*"Ovary" antiserum :*

Original uterus fluid.  
 Normal human serum.  
 { Original tonsil fluid.  
 { Original ovary fluid.  
 { Original breast fluid.  
 Normal rabbit serum.

*"Tonsil" antiserum :*

Normal human serum.  
 Original uterus fluid.  
 Original tonsil fluid.  
 Original ovary fluid.  
 Original breast fluid.  
 Normal rabbit serum.

*"Breast" antiserum :*

Normal human serum.  
 { Original uterus fluid.  
 { Original breast fluid.  
 { Original tonsil fluid.  
 { Original ovary fluid.  
 Normal rabbit serum.

The only legitimate conclusion from arranging the precipita thus is that the amount of precipitate is independent

\* Obtained from a rabbit prepared as follows :—

10—10—10—10—10 cc. injected,  
 6—3—4—2—7 days after injection.

of whether the antiserum is added to the original fluid used for the injections or not. Indeed, since the order of magnitude of the precipita is remarkably similar in the case of all the antisera tested, the magnitude of the precipitum seems to be independent of the antiserum used, but to depend upon the actual composition of the original fluid itself.

Further, it is noteworthy that the maximum amount of precipitate in two instances, and the second amount of precipitate in the two remaining instances, were given when the antiserum was mixed with normal human serum. At the opposite end of the series in point of magnitude of precipitate come mixtures of antiserum with normal rabbit serum. Although these results show that antisera prepared by injecting the juice of human new growths into rabbits contain "anti-human" precipitins, they negative the idea that such antisera may contain specific "anti-cancer" precipitins.

#### IV.—The Addition of Complement to a Mixture of Antiserum and Serum.

Owing to the fact that complement disappears after a short time from a serum, the relatively long time after killing the animals before the antisera were tested seemed to negative the supposition that complement enters into the precipitin reaction at all. Nevertheless it was desirable to test the point directly. Fresh normal rabbit serum was therefore taken and divided into two portions. One portion was added to one mixture of antiserum and normal human serum, and the other portion of normal rabbit serum was heated to 56° C. for a quarter of an hour before adding to an exactly similar mixture of antiserum and serum.

#### EXPERIMENT X.

·5 cc. antiserum ("tonsil") + ·5 cc. of 1-100 normal human serum + ·045 cc. of *heated* normal rabbit serum yielded ·0144 cc. precipitum.

·5 cc. antiserum ("tonsil") + ·5 cc. of 1-100 dilution of normal human serum + ·045 cc. of *unheated* normal rabbit serum yielded ·0128 cc. precipitum.

The presence of complement, therefore, does not lead to an augmentation of the amount of precipitum formed.



**The Properties of the Antisera as regards Hæmolysis.—**

During the process of expressing the juice from the masses of new growth it was impossible to prevent the presence of a certain amount of blood. In the case of some of the juices—particularly those which were derived from hepatic metastases—the red colour of the expressed juice was pronounced. In others it was slight, while in the case of a growth of the stomach used for injections a red colour was absent, and very few red blood corpuscles could be seen under the microscope. The “anti-tonsil” and the “anti-ovary” sera were chosen for the purpose of determining whether the antisera which contained precipitins also contained hæmolysins. The following experiment shows that the sera in question did not contain more hæmolysing power than would be explained by the presence of a small quantity of blood in the juice used for injecting the animals; while on the other hand there was evidence that an anti-hæmolysin was present in the serum.

A few drops of normal human blood were defibrinated and, after centrifugalising, the corpuscles were made into a 5% suspension in .9% salt solution. .2 cc. of this suspension were added to different strengths of normal rabbit serum, to “anti-tonsil” rabbit serum with or without complement, and to “anti-ovary” rabbit serum, also with or without complement. The results were as follows:—

Normal rabbit serum hæmolysed normal human red corpuscles when added to the latter in the proportion of 1 part of serum to 10 parts of corpuscle suspension. In dilutions weaker than this no hæmolysis appeared, and in mixtures in which the normal rabbit serum was present in greater strength than 1-10 the hæmolysis became more and marked.

Using a serum prepared by injecting a rabbit with juice expressed from a squamous cell carcinoma of the human tonsil and adding it to the same suspension of human red blood corpuscles, no hæmolysis occurred even when the serum was added to as great an amount as one-fourth of the volume of the suspension of corpuscles. A similar absence of hæmolysis was noted under the same conditions when a serum derived from a rabbit that had been inoculated with juice from a papilliferous cystadenoma of the ovary was employed.



Owing to the fact that the antisera used in the above experiments were somewhat old, it was thought that perhaps the absence of hæmolytic power depended upon the absence of complement. The experiment was therefore repeated with the addition to the mixture of corpuscles and antiserum of a quantity of fresh rabbit serum insufficient to cause hæmolysis, i.e. a quantity equal to one-twentieth of the volume of the suspension of corpuscles. In the case of the "ovary" antiserum this addition produced no change, so that it was certain that the antiserum was devoid of hæmolytic power. In the case of the "tonsil" antiserum, no hæmolysis occurred in dilutions of 1-40 and 1-20, but a trace of hæmolysis was apparent in lower dilutions. Nevertheless the amount of hæmolysis was in all degrees of dilution so slight that it was probably due to some error and was not an essential character of the antiserum.

It is not only clear from the foregoing experiments that the antisera in question were devoid of hæmolytic power, but it is also evident on comparing them with the experiment made with normal rabbit serum that they possessed the property of inhibiting a hæmolytic power residing in the normal rabbit serum. This result was so unexpected, especially as the cancer juices used for injection contained a certain number of red corpuscles, that the characters of the original fluids as regards hæmolysis were investigated. It was found that these were completely without hæmolyzing power whether fresh complement were added or not. It may be added that an antiserum made by Dr. Douglas with highly blood-stained blood serum hæmolyzed perfectly. The explanation of the results is therefore not clear; but the great destruction of red blood corpuscles that frequently occurs in cancer cases, and the occasional existence of pleural and peritoneal effusions that contain free hæmoglobin, seem to warrant the belief that a hæmolyzing substance is present in some, if not in all, cancerous tissue.

#### V.—The Microscopic Effect of the Antiserum on Cancerous Material.

Although it was found that no specific precipitin reaction was produced when the antisera prepared after the method

given above were added to the original fluids used in their production, it was thought possible that a specific reaction might nevertheless be present and recognisable on microscopic examination. Thus it was thought possible that microscopic sections of carcinomatous and sarcomatous tissue cut fresh by the freezing method and then steeped in the antisera, or steeped in the antisera in mass and then embedded in paraffin, might show different appearances, unstained or stained, from tissue that had not thus been steeped. Portions of a squamous cell carcinoma of the tongue, of a squamous cell carcinoma of the oesophagus, columnar cell carcinoma of the rectum, giant mixed cell sarcoma of the humerus, and a rodent cancer, were selected for the experiments. The specimens from the tongue and the rodent cancer were obtained fresh from the operating theatre. Small portions of the growth were placed in (*a*) normal rabbit serum, (*b*) normal human serum, (*c*) various antisera, (*d*) 50 % absolute alcohol, (*e*) Müller's fluid. The specimens in serum were kept at the room temperature for forty-eight hours, or in certain other experiments in the warm incubator for six hours. They were then removed simultaneously into, successively, 50 % absolute alcohol for twenty-four hours, 90 % alcohol for twenty-four hours, absolute alcohol, cedar oil till clear, three changes of paraffin. The small portions of tissue were cut serially and were mounted on slides, the sections themselves being in all cases  $8\mu$  in thickness. By a simple arrangement all the slides of a single comparative set were subjected to the various staining processes together, so that as far as is possible they were absolutely comparable. The stains used were chiefly hæmatoxylin (Ehrlich), with various counterstains and methylene blue.

The slides of each set of tissue were examined carefully by two different observers and on several different occasions. The mode after which the slide had been prepared was unknown until the examination was complete.

The results of this set of experiments were unsatisfactory. It was clear that all the specimens that had been exposed to the action of serum were less well defined, stained with less sharpness, and altogether formed "poorer" specimens than either those which had been at the first placed in 50 % spirit or those which had been placed in Müller.

In the case of those portions of tissue that had been exposed to the action of some variety of serum as a preliminary, very little difference was to be observed. Upon the whole the microscopical appearances of tissues that had been steeped in normal rabbit serum were not quite so ill-defined and "poor" as those which had been steeped in one or other of the antisera. But, dealing with the antisera and the different varieties of new growth, it was impossible to demonstrate the slightest evidence of selectivity. Moreover, on comparing sections from tissues that had been steeped in one or other antiserum prepared by the injection of the juice expressed from various new growths with sections of tissue that had been steeped in an antiserum prepared by injecting rabbits with *normal* human blood serum, there was equally no difference observed.

It was therefore concluded that although it is possible to demonstrate in some degree that a precipitum is formed in solid tissue by exposing it to the action of an antiserum just as in the test-tube experiment with fluids, yet the reaction in both cases is merely evidence of one common "human" reaction, and has no more restricted specificity. Whether more delicate methods would demonstrate that a real "cancerous" reaction takes place and can be used for diagnostic purposes, it is impossible to say. In view of the lack of specificity shown by the antisera prepared by Dr. Douglas and tested in a different manner, it seems improbable that such would be the case. It is, however, somewhat remarkable that so great a similarity obtains between the antisera prepared by Dr. Douglas, in which the injected material was almost entirely serum albumin and serum globulin with an almost complete absence of nucleo-proteid, and the antisera prepared by myself from the solid tissues in which nucleo-proteid was by far the largest constituent and from which serum albumin and serum globulin were almost completely absent.

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# THE PRECIPITIN REACTION IN MALIGNANT DISEASE.

(Experiments in which alkali proteids were used for preparing the antisera.)

BY HECTOR COLWELL, M.B.

THE general purport of the precipitin experiments conducted in these Laboratories is sufficiently explained on page 27 of the present volume. In the particular series of experiments now under consideration the substances employed to produce the anti-sera were as follows:—

- (1) Alkali-proteids derived from glandular metastases occurring in a case of squamous cell carcinoma of the tonsil.
- (2) Similar material derived from hepatic metastases in a case of squamous cell carcinoma of the uterus.
- (3) Alkali proteids derived from egg albumen.

The method of preparation was as follows:—

In the first two instances the masses of growth, freed as far as possible from other tissues, were finely minced and then boiled with a known quantity of  $\frac{N}{4}$  sodium hydrate solution, the mixture being meanwhile thoroughly stirred. The small masses of tissue swelled up, and the liquid became markedly viscous, but (provided the quantity of alkali used was sufficient), this viscosity soon disappeared. On continuing the boiling the solid material underwent a considerable diminution in bulk, and, when it appeared reduced as far as possible, the supernatant liquid was decanted and filtered through glass wool, the resulting filtrate being almost clear. To the filtrate so obtained, successive small quantities of  $\frac{N}{4}$  hydrochloric acid were added, the mixture being agitated after each addition, in order to re-dissolve the precipitate first produced. These additions were cautiously continued until the last-formed precipitate only just dissolved, and the resulting fluid



was very slightly alkaline to litmus. This fluid was but faintly turbid, and contained a solution of alkali proteid in physiological "saline solution," with just sufficient alkali to keep it in solution. Enough Chinosol solution was now added to produce a strength of 1 in 2000 Chinosol, and the material stored in a cold chamber. Although, when freshly prepared, only a slight turbidity was present, yet, after a stay of two or three days, in the cold chamber, flocculi appeared, which increased both in number and size the longer the fluid was stored. This condition rendered intravenous injection impossible, and, the deposit had to be broken up by shaking, to prevent blockage of the needle during intra-peritoneal injection, by which means the two first "alkali proteids" were administered.

In the case of the alkali proteids derived from egg-white, the following procedure was adopted. To 20 cc. of a  $\frac{N}{4}$  solution of sodium hydrate, which was heated upon a boiling water-bath, 5 cc of clear egg-white were added drop by drop, with constant stirring, and the whole allowed to remain upon the water-bath for half an hour. Nearly 20 cc. of  $\frac{N}{4}$  hydrochloric acid were next added in successive small quantities, as in the previous cases, and the whole made up to 50 cc with physiological "saline solution." By this last method, a clear solution was made which did not tend to produce flocculi, and which was suitable for intravenous injection.

As a control experiment one rabbit was treated (intravenously) with a dilution of 5 cc. egg-white (untreated) in 45 cc. of "normal saline" solution.

In contrast to the conditions found post mortem in animals which had been intra-peritoneally injected with expressed juice from malignant growths, it may be noted that the peritoneal cavities of animals injected with the alkali proteids before mentioned, showed no macroscopic abnormality.

The rabbits yielding the anti-sera were treated as follows:

EXPERIMENT I.—Six intra-peritoneal injections of alkali proteid derived from *glandular metastases of a case of squamous cell carcinoma of the tonsil*. The solution contained 25% by weight of the original material. Each injection consisted of 10 cc. The number of days between the injections



were 3—3—9—7—14 and the animal was killed 7 days after the last injection.

EXPERIMENT II.—Six intra-peritoneal injections of alkali proteid derived from *hepatic metastases of a case of squamous cell carcinoma of the uterus*. The solution contained 21.6% of the original material by weight. Each injection consisting as before, of 10 cc. The number of days between the injection were 4—4—2—5—3, the animal being killed 7 days after the last injection.

EXPERIMENT III.—Five intravenous injections each of 10 cc. of alkali proteid derived from *egg-white*. The solution contained 10% of the original material by volume. The intervals between the injections were 4—2—5—2 days, 10 cc. were used for each injection and the animal was killed 7 days after the last injection.

EXPERIMENT IV.—Five intravenous injections each of 10 cc. of a 10% dilution of untreated egg-white in "normal saline" solution (the same sample of original egg-white being used, as in Experiment III). The number of days between the injections were 3—4—2—2, the animal, as before, was killed 7 days after the last injection.

The two specimens of malignant growth used in this research were derived from cases used by Dr. Lazarus-Barlow in his investigation with expressed juices from cancerous materials. (Cases 6 and 7, p. 29.)

#### SERIES A.

In the first series of experiments the anti-sera derived from alkali proteids, which were made from the malignant growths, were tested against the following materials: (1) Normal human serum, (2) The original juice expressed from the hepatic metastases in the case of carcinoma of the uterus, (3) The original juice expressed from the glandular metastases in the case of carcinoma of the tonsil, (4) The original alkali proteid solution used to produce the particular antiserum, (5) The original alkali proteid solution used to produce the other anti-sera. In each case .5 cc. of the antiserum was placed in

a small test tube, and to this, .5 cc. of a 1 in 100 dilution of the liquid against which it was to be tested was added, the whole being then mixed by repeated careful inversion of the tube. It will be found convenient in the following details of the experiment to refer to the antiserum produced by injections of alkali proteids derived from the various sources, as "Anti-alk-uterus" serum, "Anti-alk-tonsil" serum, and "Anti-alk-egg" serum respectively; the fluids employed in Dr. Lazarus-Barlow's research, against which the antisera formed from their corresponding alkali proteid derivations were tested, are referred to as "expressed uterus" (or tonsil) fluid.

The results of this first series of experiments may be tabulated as follows:—

.5cc. anti-alk-uterus serum + .5 cc of 1 in 100 dilution of—

I. Norman human serum	-	-	= .0064 cc.
II. "Expressed uterus" fluid	-	-	= .0040 cc.
III. "Expressed tonsil" fluid	-	-	= .0048 cc.
IV. "Alkali uterus" fluid	-	-	= .0032 cc.
V. "Alkali tonsil" fluid	-	-	= .0032 cc.

.5 cc. anti-alk-tonsil + .5 cc. of 1 in 100 dilution of—

VI. Normal human serum	-	-	= .0048 cc.
VII. "Expressed uterus" fluid	-	-	"
VIII. "Expressed tonsil" fluid	-	-	"
IX. "Alkali uterus" fluid	-	-	"
X. "Alkali tonsil" fluid	-	-	"

The measurements in the above cases were made 48 hours after the mixture of the antiserum and the fluid against which it was tested. The differences in the amount of precipitum formed are but slight, and show no tendency to the formation of a specific precipitin (other than a generally "human" one), whether the antiserum were added to the original (diluted) alkali proteid or to the similarly treated expressed juice. The process of the formation of alkali proteids in the injection material appeared, also, to definitely reduce the formation of even an anti-human serum, as may be seen by comparing the above figures with those given on pages 35-36.

## SERIES B.

In order to provide a control for the previous series of experiments, normal rabbit serum was tested against the following fluids: (1) Original alkaline "Tonsil," (2) Original alkaline "Uterus," (3) Original fluid expressed from tonsillar growth, (4) Original fluid expressed from uterine growth, (5) Original diluted egg-white, (6) Original solution of alkali proteid derived from egg-white.

In none of these cases was any precipitate obtained, and thus the precipitates obtained in the previous experiment must be regarded as definitely due to formation of a weak antiserum by the injection of the alkali proteids.

In the case of the animal injected with a 10% dilution of untreated egg-white, .5 cc. of the antiserum, when tested against a 1 in 100 dilution of the original fluid gave a good precipitate (.0192 cc.) when measured after 48 hours. A similar quantity of the same antiserum when tested against a 1 in 100 dilution of the original alkali egg-white solution produced only a very small amount of precipitate (.0032 cc.) when measured after a similar period.

## CONCLUSIONS.

(1) That the substance produced by treatment of new growths with dilute alkali and subsequently with dilute acids, only yields a small amount of an anti-serum upon injection into rabbits.

(2) That this antiserum has no specific, and only ill-marked "anti-human" characteristics.

(3) That no specific antiserum is produced for alkali proteids, prepared in the manner described.\*

(4) That the proteid constituents of new growth do not deviate from the rule, that treatment of the original material with acids hinders the formation of an antiserum.

\* This is in accordance with the work of Michaelis and Oppenheimer upon the subject, who have found that treatment of the injection material with even traces of acid hinders the formation of an antiserum capable of producing a precipitate with the original fluid. Quoted by Hunter "Journ. Physiology," 1905.

# CONTRIBUTION TO THE STUDY OF THE BLOOD IN MALIGNANT DISEASE.

## II.—THE QUESTION OF THE FORMATION OF SPECIFIC PRECIPITINS.

By J. J. DOUGLAS, M.D., F.R.C.P.E.

IN planning the experiments described below the following was assumed as a working hypothesis. Cancer cells in the course of their metabolism give rise to a substance which is toxic to the organism. The fact that cancer kills seems to prove that there is something produced and given off by the new growth which causes toxæmic cachexia, and ultimately death. For the purpose of convenience let this something be called cancer toxin, and, as we assume that it exists, must it not be present in the tissues and fluids of the body? If then an animal (rabbit) be treated with a cancer-toxin-containing fluid, certain anti-substances will be found in its blood. These will fall into two groups: (1) those *anti* to substances (proteids) normal to the fluid; and (2) those *anti* to its abnormal substances (cancer toxin). If this is the case, such an anti-serum would with serum from a case of cancer (cancer-toxin-containing serum) form a precipitum (1) *quâ* the normal proteids of the serum, and (2) *quâ* its abnormal cancer toxin. This precipitum would be on this account larger in bulk than that produced by the reaction with the same cancer-serum of an antiserum obtained by the treatment of an animal with a similar fluid containing only its normal constituents, the anti-cancer toxin precipitin being in this latter case absent. Similarly, too, the former antiserum would be expected to give a greater precipitum with cancerous than with normal fluid (serum).



*Description of Material employed.*

*ANHS* = anti-normal human serum. This antiserum was obtained by intravenous injection into a rabbit (♀) of—

*NHS* = normal human serum. This serum was obtained by venesection from a case of heart disease.

The details of the preparation of the antiserum are as follows:—

$$1.1-1.1-1.1-2.3-3-4.1-4.1 = 16.8 \text{ cc.}$$

$$1-1-5-1-4-2-14 = 28 \text{ days.}$$

(It was found to give a good reaction after the third injection.)

*ACHS* = anti-cancer-human serum. This was prepared by intravenous injection into a rabbit (♀) of peritoneal fluid obtained from P.M. room from a case of cancer of the uterus, with secondary infection of the peritoneum.

The details of its preparation are as follows:—

$$1.1-2.2-3-2-3 = 11.3 \text{ c.c.}$$

$$3-1-4-2-14 = 24 \text{ days.}$$

*CHS* = Cancer-human serum. This was obtained from operating-room from a case of cancer of the breast.

## EXPERIMENT 1.

*ANHS* + *CHS* and *ACHS* + *CHS*.

1. *ANHS* + *CHS* (.4 cc. + 2 cc. (1-100)).

- a. Next day: fair precipitum (estimated after 24 hours as .0266 cc.)

The tube was centrifuged and the supernatant fluid pipetted off several times. To this supernatant fluid .4 cc. *ANHS* were added.

- β. Next day: very slight precipitum.

The tube was again centrifuged and the supernatant fluid pipetted off.

To this supernatant fluid .4 cc. *ACHS* was added for contact reaction.

- γ. Next day: indistinct contact reaction with slight precipitate at bottom of the tube.



## 2. ACHS + CHS (4 cc. + 2 cc. 1-100).

a. Next day: fair precipitum (estimated after 24 hours as .0266 cc.).

The tube was centrifuged, and the supernatant fluid pipetted off several times. To this supernatant fluid 4 cc. ACHS was added.

$\beta$ . Next day: very slight precipitum.

The tube was again centrifuged, and the supernatant fluid pipetted off. To this supernatant fluid 4 cc. ACHS was added for contact reaction.

$\gamma$ . Next day: indistinct contact reaction with slight precipitate at bottom of the tube.

In planning this experiment it was thought possible on the hypothesis stated, that at 1 $\gamma$  the reaction would be distinctly more marked than at 2 $\gamma$ , on the assumption that by steps 2a and 2 $\beta$  the normal proteids of the CHS + its cancer toxin had entered into the formation of the precipitum, whilst by steps 1a and 1 $\beta$  only the former of these two sets of substances had taken part in the precipitum. At 1 $\gamma$  then the supernatant fluid was expected to be free from precipitable normal proteids, but to contain cancer toxin, while in 2 both precipitable normal proteids and cancer toxin were assumed to have been precipitated by steps a and  $\beta$ . The results, however, were wholly disappointing in this regard, being in 1 and 2 identical, even as to the bulk of the precipitum at a. The indistinct contact reaction at  $\gamma$  is regarded as negligible.

If one adheres to the initial hypothesis, it may be that the cancer toxin has been entangled in some way with the precipitable normal proteids, and so brought down with them.

## EXPERIMENT II.

## ACHS + OF and ANHS + OF.

In this experiment the original fluid [OF], peritoneal fluid, used in the preparation of ACHS was employed.

## 1. ACHS + OF (2 cc. + 1 cc. (1-4)).

Next day: a good precipitum, estimated as .1583 cc.

Supernatant fluid + 2 cc. ACHS.

Next day: small precipitum, estimated as .0109 cc.

---

.1683 cc.

## 2. ANHS + OF (2 cc. + 1 cc. (1-4)).

Next day : a good precipitum, estimated as .1600 cc.  
(but rather loose)

Supernatant fluid + .2 cc. ANHS.

Next day : small precipitum, estimated as . . . . . .0116 cc.  
.1716 cc.

These results may be considered identical. Instead of there being a greater precipitum with ACHS, it was, if anything, the other way.

The same may be said of the results of the next experiment, although it has not the same significance, serum from a case of sarcoma of the parotid being used.

## EXPERIMENT III.

ACHS and ANHS + serum from a case of sarcoma of parotid.

## 1. ACHS + serum (.4 cc. + 2 cc. (1 in 100)).

Next day : precipitum = .0450 cc.

## 2. ANHS + serum (.4 cc. + 2 cc. (1 in 100)).

Next day : precipitum = .0475 cc.

In the next experiment the reactions of ACHS and ANHS with NHS were compared.

## EXPERIMENT IV.

ACHS + NHS and ANHS + NHS.

## 1. ACHS + NHS (.4 cc. + 2 cc. (1 in 100)).

Next day : fair precipitum, estimated after  
24 hours as . . . . . .0250 cc.

Centrifuged and supernatant fluid treated  
with .4 cc. ACHS.

Next day : considerable precipitum, estimated after 24 hours as . . . . . .0275 cc.  
.0525 cc.

Centrifuged and supernatant fluid treated  
with .4 cc. ACHS (contact).

Next day : slight but distinct reaction.

## 2. ANHS + NHS (4 cc. + 2 cc. (1 in 100)).

Next day: fair precipitum, estimated after  
24 hours as . . . . . 0241 cc.

Centrifuged and supernatant fluid treated  
with 4 ACHS.

Next day: considerable precipitum, esti-  
mated after 24 hours as . . . . . 0283 cc.

0525 cc.

Centrifuged and supernatant fluid treated  
with 4 cc. ACHS (contact).

Next day: slight but distinct reaction.

The results in this case were identical.

These experiments suggest that by the methods followed at any rate a precipitin specific to cancer is not likely to be demonstrated. It may be that the "anti-cancer" serum obtained contained so much "anti-normal" material that a possible specific reaction was masked.

Both Engel,\* to whose valuable paper I am much indebted, and Martens,† working on the same lines, obtained inconclusive results.

\* Deutsch. med. Wochenschr., No. 48, '03.

† *Ibid.*, No. 6, '04.

# ON LYMPHATIC PERMEATION AS A FACTOR IN THE DISSEMINATION OF MELANOTIC SARCOMA, WITH A NOTE ON OPERATIVE TREATMENT.

By W. SAMPSON HANDLEY, M.S.LOND., F.R.C.S.

## I. INTRODUCTORY.

THERE are certain exceptions to the rule that sarcomata do not invade the lymphatic glands. In sarcoma of the testis and of the tonsil, in lympho-sarcoma, and in melanotic sarcoma wherever it is situated, the lymphatic glands are frequently involved. Clearly therefore the lymphatic channels are concerned in the dissemination of these exceptional forms of sarcoma.

The investigation now to be described was undertaken with two objects, firstly, to determine what share lymphatic spread takes in the dissemination of sarcomata which are prone to invade lymphatic glands; and secondly, to find whether the process of permeation, which I have described as taking a predominant part in the dissemination of carcinoma,\* can also be detected in such sarcomata. Sarcoma of the melanotic variety was chosen for investigation because its commonly intense black colour renders the unequivocal recognition of very minute foci of growth easy both to the naked eye and microscopically. Moreover, this variety of sarcoma, frequently arising in regions whose lymphatics are tributary to the fascial lymphatic plexus, often gives rise, like carcinoma of the breast, to subcutaneous nodules; and an accurate comparison of the mode of spread of these two varieties of growth in identical tissues thus becomes possible.

Owing to the rarity of melanotic sarcoma, and the somewhat tedious method of investigation employed, this paper deals only with one case.

\* See Archives of the Middlesex Hospital, vol. v.

## II. DETAILED DESCRIPTION OF CASE.

**Abstract of Necropsy.**—Necropsy No. 186, The Middlesex Hospital, 1905. The body is that of an emaciated woman, aged thirty-four. At the insertion of the right tendo Achillis is a small healthy linear scar, where the primary melanotic sarcoma was excised. In Scarpa's triangle on the right side is a considerable mass in the situation of the femoral glands. Beneath the skin over and around this mass are very numerous discrete black nodular growths, occupying an area roughly circular in shape and perhaps eight inches in diameter (see Fig. 1). The growths become smaller in all directions the further they are situated from the femoral glands, until apparently healthy skin is reached.

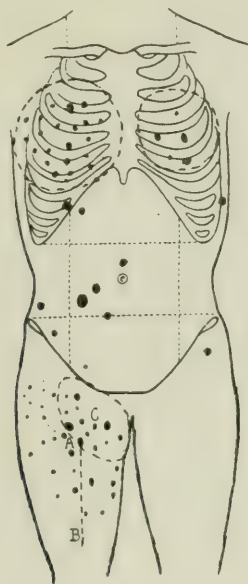


FIG. 1 shows all the visible subcutaneous nodules of melanotic growth present in the anterior aspect of the body, except one on the face.

The dotted line A B shows the position and extent of the strip of tissue removed for examination. The dotted circles in the mammary region represent prominent masses of secondary growth in the breasts.

Note that the growth was on the right heel, and that most of the secondary nodules are situated on the right side of the body.



On the back, at the level of the tenth dorsal vertebra, there is a patch three inches square studded with similar cutaneous growths.

The right breast shows enormous enlargement, and in the skin over the breast are many similar growths. The left breast, though smaller, is in a like condition. Scattered over the front of the thorax and the abdomen are numerous subcutaneous nodules, and there is one on the face in the left malar region. There is far more growth on the right side of the body than on the left. No deposits are present in the skin and subcutaneous tissue of the left leg below the level of the symphysis pubis.

There are numerous deposits in the calvaria; a few small nodules are present in the brain, and in the thyroid body.

Several deposits are found on the posterior surface of the sternum. The cardiac muscle contains numerous nodules, and a few are scattered throughout the lungs.

The liver weighed  $101\frac{1}{2}$  ounces. The only abdominal viscera free from new growth are the spleen, ureters, bladder, and stomach. Numerous nodules are pendent from the mucosa of the intestines.

The left femur shows a fracture one inch below the great trochanter, surrounded by a mass of non-pigmented new growth. All the muscles examined show minute specks of melanotic pigment. As regards the lymphatic glands, growth is found in the right femoral and internal iliac glands (and to a less extent in the lumbar glands), and in the cervical and axillary glands on both sides.

For the investigation of lymphatic spread in this case it was natural to choose the tissues in the neighbourhood of the largest mass of lymphatic glands, that is to say, the tissues of the right groin. A strip of the parietal tissues passing down the thigh from this mass of glands was removed for examination.

**Naked-eye Description of Strip.**—The strip of tissues examined measured 17 cm. in length, and extended from the lower edge of the mass of growth which occupied the situation of the inguinal glands vertically down the anterior surface of the thigh to a point about 3 in. above the knee. It traversed

and passed well below the circum-inguinal area of visible subcutaneous nodules of growth (see Fig. 1).

The strip included skin, subcutaneous fat, deep fascia, and a thin layer of muscle. It was frozen, and subdivided longitudinally into three thinner strips. One of these was submitted to microscopic examination, while the two other strips, each about 3 mm. thick, were mounted as naked-eye specimens.

*Method of Preparation.*—The strips were prepared by a modification of a method which I first employed in 1904 for demonstrating carcinomatous nodules in the parietal tissues in cases of breast-cancer. For this purpose long strips of the skin and subjacent parietal tissues radiating in any selected direction from the primary growth were cut from the cadaver, and were subsequently stained and rendered translucent.\*

The staining method employed had the defect common to all stains, that it is not specific for cancerous tissues. Moreover time has shown that the specimens, when mounted in xylol for preservation in a museum, undergo continuous shrinkage, and lose their purity of colour, so that after the lapse of two years their deterioration is marked.

Melanotic sarcoma offers an ideal field for the application of this method in a simplified form, because the specimens can be mounted in an absolutely unstained condition. The dark colouration of this particular variety of growth is the equivalent of a specific stain for malignant tissues, a desideratum which is at present lacking in the case of other growths.

The two strips having been frozen and cut, were placed in methylated spirit for twelve hours, and subsequently in acetone for a similar period; they were thence transferred to xylol for a few hours, and finally mounted in liquid paraffin (parolein, B. W. & Co.) as museum specimens in flat-sided jars.

The use of acetone as a dehydrating agent in place of absolute alcohol was suggested to me by Dr. Victor Bonney, while the employment of liquid paraffin as a mounting fluid

\* The original method is described in Archives of the Middlesex Hospital, vol. iii., 1904. A coloured drawing of a specimen prepared by this method will be found in the Glasgow Medical Journal for December, 1905.

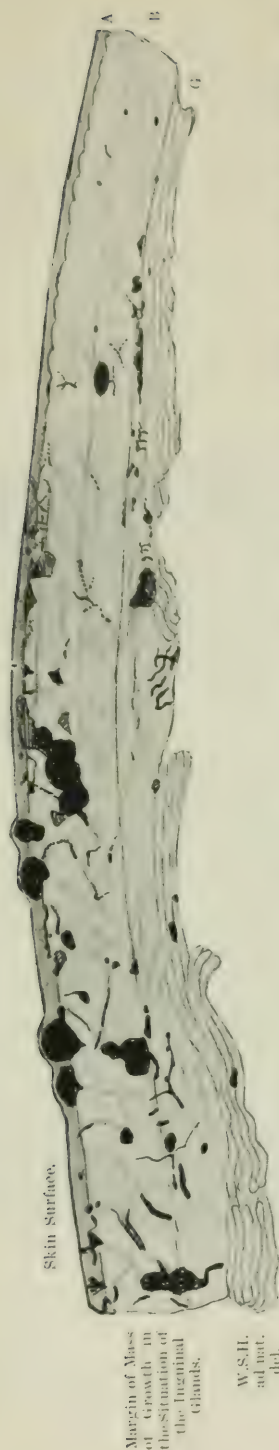
is an improvement due to Mr. Cecil Rowntree. In contrast to xylol, liquid paraffin is not appreciably volatile; moreover, it is perfectly transparent, and tends rather to make the specimen soft and pliable than to harden it. The only remaining doubt, whether it ultimately exercises any deleterious influence on the specimen or is itself discoloured by the action of light, can only be settled by the lapse of time.

*Naked-eye Description of Radial Strip.*—Subject, of course, to microscopic confirmation, the strip affords to the naked eye a beautiful demonstration of the process of permeation (see Fig. 2). At the proximal end of the strip the translucency of the tissues is blurred by an abnormal excess of adventitious fibrous tissue in the subcutaneous fat, an index to the inflammatory reaction excited by the growth. Here large nodular masses and cords of growth are seen in the various layers, but the finer network of black lines seen towards the distal end of the strip is absent.

The salient features of the strip may be best expressed in the following table of measurements, which are all taken from the upper end of the strip:—

	Centimetres.
Total length of strip . . . . .	17
Retiform (intravascular) invasion of deep fascia and deepest layers of the subcutaneous fat present in the entire length . . . . .	17
Nodular invasion of the deep fascia . . . . .	13·6
Retiform (intravascular ?) invasion of the skin . . . . .	12
Nodular invasion of the skin . . . . .	10
Nodular invasion of the muscle . . . . .	9·5
Nodules forming palpable and visible prominences on the skin surface . . . . .	6·5

**Microscopic Description of Strip.**—The various blocks into which the original strip was divided will now be described in order from the proximal to the distal end. It will be noted that a gradual and regular change takes place as the strip passes under review. At the proximal end are large nodules, with invasion of the arteries and veins as well as the lymphatics. At the distal end no invaded blood vessels are to be found, nor are large nodules of growth present; but the lymphatics are filled by fine cylinders of growth.



Margin of Mass  
of Growth in  
the Situation of  
the Inguinal  
Glands.

W.S.H.  
ad. 1896.  
del.

FIG. 2. —Drawing, natural size, of a translucent strip of the skin and underlying tissues taken in a radial direction from the mass of growth in the situation of the inguinal glands, to demonstrate the centrifugal spread of permeation. Note that the growth extends much further along the deep fascia than along the skin or in the muscle.

A, skin ; B, subcutaneous fat, separated by the deep fascia from G, a thin layer of muscle.



The presence of inflammatory changes at the proximal end of the strip, and their absence at the distal end, are to be especially noted, as indicating that a process analogous to the "perilymphatic fibrosis," which obliterates permeated carcinomatous lymphatics, occurs also in melanotic sarcoma.

*Block 1.*—In this block there is invasion of arteries and veins, together with nodular invasion of the tissues; but there is no reticulum of small permeated lymphatics. It is probable that many of the originally permeated lymphatics have been destroyed by perilymphatic fibrosis, for at this, the proximal

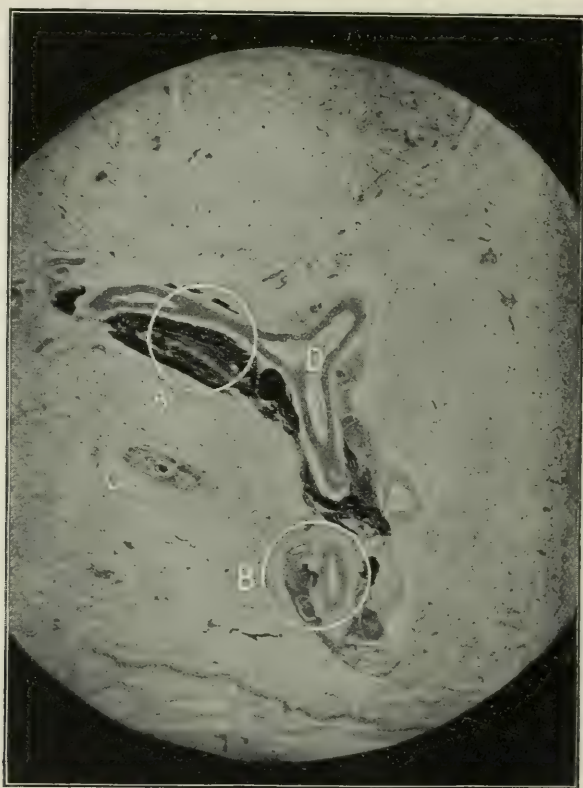


FIG. 3,  $\times 30$ , from the proximal end of the strip near the mass of growth which represented the inguinal glands, shows a cylindrical cord of melanotic growth, lying unencapsuled in the periarterial tissues, and replacing the comitant venous and lymphatic vessels.

D is the artery, C a small vein containing a cylinder of degenerate growth infiltrated by leucocytes. The circles A and B indicate the situation of Figs. 4 and 8.



end of the section, the subcutaneous tissues appear even to the naked eye to be abnormally rich in adventitious fibrous tissue.

*Muscle*.—Absent from the section.

*Deep Fascia*.—Only one focus of growth is present, a cord which probably represents a large lymphatic, for it lies not far from a normal small artery and vein.

*Subcutaneous Tissues*.—In the deeper subcutaneous fat is a normal artery of considerable size, accompanied by a cord of growth (see Fig. 3), which certainly represents the vein, for in it can be seen embedded remains of muscular



FIG. 4,  $\times 160$ , represents highly magnified the upper circle A in Fig. 3. Above is seen in oblique section a normal artery A A. Accompanying this artery and below it is a cord-like cylinder of growth G G G. That G G G represents the vein which originally ran with the artery is shown by the presence within it of a well-marked band of unstriated muscle M M, doubtless a relic of the wall of the vein, which itself was invaded originally from adjacent permeated lymphatics (see Fig. 5).

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tissue (see Fig. 4). This cord probably replaces also the comitant lymphatics of the artery in question.

More superficially is an artery, unaccompanied by a vein, which lies in the plane of the section for a considerable distance. It is more or less filled along the whole of its visible portion, with melanotic growth. It is directed towards a region where two nodules of macroscopic size lie in the subcutaneous fat a little distance below the skin.

Some very minute foci of obsolescent growth, enveloped in inflammatory round cells, are present in the fibrous periarterial tissues.

The fibrous septa which join the skin to the deep fascia, besides presenting one or two minute foci of vigorous sarcoma cells, are littered along their length with fine granules of melanotic pigment, and with very degenerate but still recognisable sarcoma cells.

*Skin.*—The skin invasion is not uniform, but has occurred at points where the fibrous septa join it. The terminal subdermal expansions of these fibrous septa are densely infiltrated by sarcoma cells.

*Block 2.*—No arterial invasion is present in this block. Otherwise the appearances are similar to those in Block 1.

*Muscle.*—Absent from the section.

*Deep Fascia.*—One or two groups of sarcoma cells, densely enveloped by inflammatory round cells, are present in the deep fascia. A larger aggregation of sarcoma cells, which has slightly infiltrated the overlying fat, is in an advanced stage of degeneration, and in places shows actual infiltration by inflammatory cells.

*Subcutaneous Tissue.*—The most prominent object in the subcutaneous fat is a large macroscopic nodule of growth, in parts degenerate and penetrated by round cells. Embedded in the centre of this mass are two small arteries, whose muscular coats show commencing infiltration by the growth which surrounds them. The lumen of these vessels is free from growth.

Other smaller nodules of growth are present in the subcutaneous tissues, along the course of the fibrous septa. One minute cord-like mass of growth is very degenerate. Its cells stain badly, and it is both surrounded and infiltrated by

deeply-stained round cells. This focus probably represents an intermediate stage in the process of perilymphatic fibrosis, which had destroyed the smaller permeated lymphatics of the two sections 1 and 2.

*Skin*.—The skin of this section presents three large nodules of deeply pigmented growth. In addition to these nodules the sub-dermal expansions of several of the fibrous septa show infiltration by degenerate growth, with dense collections of leucocytes around the invaded septa.

*Block 3*.—The characteristic feature of this section is the large number of inflammatory round cells which are present. They are not diffused throughout the tissues, but are localised in large numbers both in the blood-vessels and also in the perivascular tissues.

*Muscle*.—Absent from the section.

*Deep Fascia*.—Absent from the section.

*Subcutaneous Fat*.—In the deepest layer of the subcutaneous tissue is an artery partially filled by growth. The muscular coat is in places infiltrated in its whole thickness by sarcoma cells. Outside the artery are a few recognisable sarcoma cells mixed with round-celled infiltration. The appearances are consistent either with embolism and infiltration of the arterial wall from within, or with penetration of its wall from an adjoining permeated lymphatic which has subsequently undergone fibrosis.

At various points along the fibrous septa are seen in transverse section relatively large thin-walled vessels lined by endothelium. They possess no definite muscular wall, and are filled by growth. Almost certainly they represent distended lymphatics.

Here and there are small dense localised collections of leucocytes. In some of these aggregations a few degenerate sarcoma cells and melanin granules can be distinctly recognised.

*Skin*.—The skin contains two large nodules of growth. It is also in places microscopically infiltrated, but not along its whole length.

*Block 4*.—This block, like the preceding one, shows large numbers of inflammatory round cells in and around the blood vessels.

*Muscle, Deep Fascia*.—Absent from the section.

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*Subcutaneous Tissues.*—Near the deep fascia is a large artery with a group of sarcomatous cells lying free in the lumen. Towards the other end of the section are a normal small artery and vein, accompanied by a cord of growth which appears to represent a lymphatic. The middle layer of the subcutaneous tissue is occupied by large confluent nodules of growth. The terminal sub-dermal expansions of two of the fibrous septa are infiltrated by growth.

*Skin.*—The skin is practically free from growth, showing merely one or two endothelial spaces (distended lymphatics) containing sarcoma cells.

*Block 5.*—Exudation of round cells is still present, but to a much less extent than in the preceding sections. The arteries in the section are normal.

*Muscle.*—A thin layer of muscle, which forms the lower margin of the specimen is entirely free from growth.

*Deep Fascia.*—Five foci of growth are spaced out along the deep fascia. They lie within small endothelial-lined spaces, some of which are cut longitudinally, others transversely. Normal blood-vessels can in places be seen closely adjacent to these spaces, which undoubtedly are lymphatics.

*Subcutaneous Tissues.*—Intravascular foci of growth, in places beginning to infiltrate [the surrounding tissues, are sparsely scattered along the fibrous septa of the subcutaneous fat. The vessels containing these foci are very thin-walled, and possess no definite muscular tissue. A slight excess of round cells is present in the perivascular tissues. No large nodules are present in the section.

*Skin.*—A layer of skin is not present along the whole length of the section. At one point, where a fibrous septum runs up to the dermis, there is commencing interstitial infiltration of the fibrous tissue of the dermis. A large permeated lymphatic is present near this point.

*Block 6.*—A small series of sections was cut from this block. No invaded blood vessels were found in it anywhere.

*Muscle.*—The muscular layer was free from growth.

*Deep Fascia.*—About thirteen small foci of growth were spaced out at intervals along the course of the deep fascia, lying either upon its surface or in its substance. Most of these foci appeared to represent small lymphatic vessels, but



their endothelial lining was not clearly traceable. One large endothelium-lined space, without any muscular tissue in its wall was clearly recognisable as a lymphatic. It contained a mass of degenerate growth, penetrated almost throughout by inflammatory round cells, which were also present in abnormal numbers just outside its wall. Not far from this large lymphatic a small artery and vein, both normal and seen in cross section, were accompanied by two permeated lymphatics containing vigorous sarcoma cells. An exactly similar focus of growth—a normal artery and vein with two permeated lymphatics—is present on the other side of the large lymphatic described earlier (see Fig. 6). There is a moderate amount of perilymphatic leucocytosis round some of the permeated fascial lymphatics.

*Subcutaneous Fat.*—Here and there in the course of the fibrous septa minute cords of growth are seen cut across either transversely or obliquely. There seems to be an excess of fibrous tissue around these foci, and many round cells are present—not only in the immediate neighbourhood but actually within the sarcomatous tissue. These cords of growth appear to represent permeated lymphatics in an early stage of fibrosis.

*Skin.*—The dermis shows slight infiltration at one or two points in its deepest layer.

*Block 7.*—This section, like the preceding one, is characterised by the presence of numerous intravascular (intralymphatic) foci of growth spaced out along the whole length of the deep fascia, while the subcutaneous tissue is relatively free from growth. There is no excess of round cells in the tissues.

*Muscle.*—Only a few shreds of muscle are present in the section. They are free from growth.

*Deep Fascia.*—About six foci of growth, consisting either of groups of endothelium-lined spaces full of sarcoma cells, or of minute nodules lying in the tissues, are present along the deep fascia. At the proximal end of the section there is a nodule of non-pigmented growth which envelops a small artery and is infiltrating its wall. The vessel contains normal red corpuscles. Next comes a group of minute branching spaces containing growth, lying between the fibrous bundles of the deep fascia. Some of these are lined by definite



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endothelium. These are succeeded, as the section passes under review, by a small nodule of growth which is beginning to infiltrate the fat overlying the deep fascia. Next comes a small normal artery, seen in longitudinal section, accompanied by minute cords of growth, which in places lie definitely within endothelial walls. A normal vein is seen in cross section close to the artery. A normal vein is seen in cross section close to the artery.

*Subcutaneous Fat.*—There is very little growth in the subcutaneous fat. Five or six foci are present, all minute. Some of these lie free in the tissues, others are enclosed in thin endothelial walls. The arteries and veins appear normal.



FIG. 5.—From block 8, close to the deep fascia. 1 in. obj., No. 8 oc.

At this point the growth has permeated the lymphatics and is infiltrating the tissues around, but has not yet penetrated to the interior of the blood-vessels.

A is an artery, B a vein, both normal. C is an endothelium-lined space (lymphatic), permeated by growth which has burst through its walls. D is a permeated lymphatic whose wall is still unruptured.

*Skin.*—The skin is absent from the section except at one point, where a group of sarcoma cells lie within a space in the dermis, probably a lymphatic.

*Block 8.*—Inflammatory changes are almost entirely absent, that is to say, there is slight, if any, excess of round cells in the tissues.

*Muscle.*—At one point, about the middle of the section, there is a microscopic collection of sarcoma cells just beneath the surface of the muscle, which is elsewhere free from invasion.

*Deep Fascia.*—At the proximal end of the section there is a microscopic nodule of diffuse growth which has infiltrated the deep fascia to its deep surface. Opposite the point where the intravascular focus is situated there is a collection of sarcoma cells just beneath the deep fascia. At each of two other foci lying just superficial to the deep fascia (Fig. 5), the growth has infiltrated the walls of two permeated lymphatics, and is beginning to envelop the artery and vein which accompany them. The three other foci of growth present upon the deep fascia are definitely intravascular. Near one of these foci normal minute blood-vessels are visible. There can, therefore, be no doubt that the invaded vessels are lymphatics.

*Subcutaneous Tissue.*—The subcutaneous fat presents only two minute foci, one of which is beginning to infiltrate the fat, the other is apparently intralymphatic. No invaded arteries or veins are present.

*Skin.*—The skin is absent from this section.

*Block 9.*—No invaded blood-vessels are present.

*Muscle.*—The layer of muscle present is free from growth.

*Deep Fascia.*—Two intravascular foci of growth are present upon the deep fascia. These foci are cross-sections of permeated lymphatics. Close to them a normal small artery and vein are visible. Very few leucocytes are present in the neighbourhood (see Fig. 7).

*Subcutaneous Tissue.*—Two microscopic foci, not definitely intravascular, are present in the subcutaneous tissue.

*Skin.*—The skin is wanting at this, the distal end of the strip examined.

### III.—A DISCUSSION OF THE DATA RECORDED IN SECTION II.

#### **Local Dissemination Around the Right Inguinal Glands.**

The spread of subcutaneous nodules in all directions from the invaded mass of inguinal glands (see Fig. 1), indicates the working of a process of local centrifugal spread from point to point around these glands. The nature of this process is made clear by the microscopic findings which have just been described. Its various stages, from the most advanced to the earliest, are seen successively as the selected radial section is traced outwards from the centre of the mass of glands. Since the strip was taken down the limb, and therefore against the flow of lymph, the force of the lymph-stream can have taken no share in this process of local centrifugal dissemination, at any rate in the particular radial section examined.

It is obvious, both from Fig. 2 and from the microscopic sections, that the process is one of continuous growth of sarcoma along the vessels. And since towards the distal end of the strip only the lymphatic vessels are invaded, and the blood-vessels are normal, it is clear that lymphatic permeation is the initial process in the local centrifugal dissemination which we are discussing, and that invasion of the blood-vessels—present only at the proximal end of the strip—is a secondary consequence in point of time, though not in point of importance.

#### **Invasion of Blood-vessels from Comitant Permeated Lymphatics.**

The tendency of melanotic sarcoma to spread along the perivascular tissues immediately outside the blood-vessels has been noticed by Borst. His explanation of the fact is a teleological one, namely, that blood is a necessary food for the production of melanin, and that consequently the sarcoma cells are attracted towards the blood-vessels by a kind of chemiotaxis. The true explanation appears to be a simple anatomical fact. The lymphatic vessels, along which permeation extends, usually run in company with arteries and veins.

Figs. 3, 4, 5, 6 and 7, show the various events which lead to the invasion first of veins, and later of arteries, from comi-

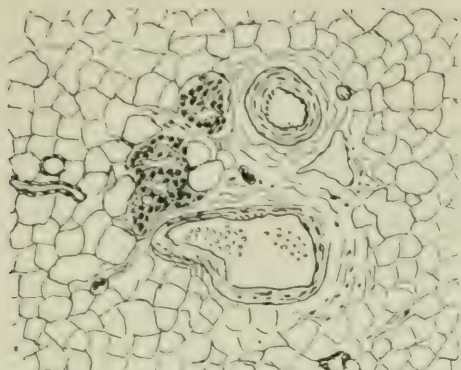


FIG. 6.—From block 5, close to the deep fascia,  $\frac{3}{8}$  obj. No. 8 ocular.

A normal artery and vein are accompanied by two microscopic cords of growth, which doubtless represent their comitant lymphatics.

To show that lymphatic invasion precedes invasion of the blood-vessels.

tant permeated lymphatics. In Fig. 7, taken from the distal extremity of the strip (block 9), a permeated lymphatic is seen lying near a small artery and vein. Fig. 6 (block 5) shows two permeated lymphatics lying near normal blood-vessels. Fig. 5 shows the rupture of permeated lymphatics and the proliferation of the sarcoma cells around the walls of the accompanying artery and vein. In Fig. 3 the vein has been infiltrated and destroyed by sarcoma, and portions of its muscular wall are embedded in a cord of growth which accompanies the

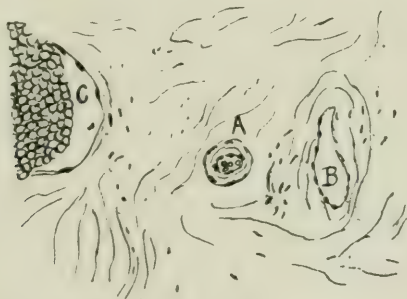


FIG. 7.—From block 10,  $\frac{3}{8}$  obj. No. 8 ocular.

The remotest fascial focus present in the strip represented in Fig. 2. A is an arteriole containing blood corpuscles, B is a venule. Both are free from growth.

C is a mass of sarcomatous tissue, circular in section, bounded on one side by a space lined by endothelium, which appears to be a ruptured lymphatic.

No invaded blood-vessels were present anywhere in the slide from which this section was taken. Lymphatic invasion is thus shown to precede blood-invasion.



artery. The artery itself remains intact. The last stage of the process is demonstrated in another field of the same slide, where an artery filled by growth can be seen.

### **The Question of Spread along the Skin.**

A glance at Fig. 2 shows that the skin is not invaded nearly so widely as the deep fascia. As in carcinoma of the breast, the question arises how invasion of the skin occurs. Does the growth spread along the hypothetical "deep cutaneous" lymphatic plexus at the junction of the dermis with the subcutaneous fat, as was formerly assumed to be the case in breast cancer? Between points situated 10 and 12 cm. along the strip a definite meshwork of black lines in this place can be seen (Fig. 2), and a superficial glance suggests that this network is the permeated "deep cutaneous plexus," and that the growth is in fact spreading slowly in this plane as well as in the plane of the deep fascia.

Closer inspection shows the error of the supposition. Just beyond the furthest point of invasion of the skin, the growth is seen creeping up to the skin from below, against the lymph stream, along the vertical tributaries which convey lymph from the skin to the lymphatic plexus of the deep fascia. The fallacious appearance of a permeated deep cutaneous plexus is evidently only a further stage of this process. As Sappey showed, the lymphatic vessels coming from the skin, though they freely interlace, do not at the deep aspect of the dermis form a true plexus. They simply interlace like the entangled boughs of adjacent trees in a thick wood. The only cutaneous lymphatic plexus is the sub-papillary plexus.

As in carcinoma, the layers adjoining the plane of the main (deep fascial) lymphatic plexus, are attacked by the upstream extension of permeation along the tributary lymphatics of the fascial plexus.

### **Regressive Changes in Melanotic Sarcoma.**

On reading the detailed microscopic description of the strip described on pp. 56-65, it is obvious that three zones can be distinguished: (a) A proximal zone where permeated lymphatics have been to a large extent destroyed. In this zone much adventitious fibrous tissue is present. (b) A zone char-



acterized by the presence of large numbers of round cells, around the sarcomatous foci and within the vessels. (c) A distal zone where no inflammatory reaction to the process of permeation has yet taken place. It thus appears that reparative processes, inadequate for cure, are not absent in melanotic sarcoma. Lymphatics and veins permeated by melanotic sarcoma may undergo destruction if the patient lives long enough. Although the mere presence of sarcomatous elements in normal tissues does not excite any inflammatory reaction, yet when the sarcoma cells become degenerate or exert



FIG. 8,  $\times 160$ , represents highly magnified the lower circle B in Fig. 3, and illustrates the reparative processes which occur even in very malignant growths. A is a normal artery, G a mass of growth lying in a space without definite walls, which may be an artefact of the hardening process, but in any case probably represents a ruptured lymphatic or vein. The growth G is surrounded by a very dense collection of inflammatory round cells R. In other parts of the section from which Fig. 8 is derived the later stages of perilymphatic fibrosis could be traced.

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mechanical pressure, an inflammatory reaction occurs, which may end in the encapsulation and destruction of the sarcomatous tissue. Even metastases visible to the naked eye may probably in this way be occasionally destroyed. Borst has already drawn attention to the regressive changes which may occur in melanotic sarcoma. Fig. 8 (page 69) shows a dense mass of inflammatory round cells surrounding and destroying a focus of growth.

### **Conclusions from Examination of the Tissues in the Inguinal Region.**

1. From the fairly regular distribution of skin nodules around the embolically invaded right inguinal glands, it may be inferred that a process of local centrifugal spread independent of the direction of the lymph current, took place around these glands as a focus.

Examination of a radial strip of the parietal tissues extending from these glands showed:—

2. That permeation of the lymphatics is the principal agent in this local centrifugal spread, and that it occurs primarily and most extensively in the plane of the deep fascial lymphatic plexus.

3. Invasion of skin and muscle is due to up-stream permeation of the lymphatics which carry lymph from these layers to the fascial lymphatic plexus.

4. Owing to the fact that arteries and veins usually run in close contiguity to lymphatic vessels, lymphatic permeation is followed by infiltration of the walls of veins, and later of arteries, and by intrusion of the growth into the lumen of the blood-vessels. The importance of invasion of the veins with regard to pulmonary and systemic dissemination is obvious.

5. The order in time of these various events is deduced from the orderly sequence of processes seen as the strip of tissues is traced from its distal end towards the mass of glands which formed the local centre of infection.

6. Regressive changes, due to inflammation excited by the growth, may occur in melanotic sarcoma.

**The Share of Embolism in producing the Metastases.**

The direct evidence that the majority of the skin nodules present did not originate from emboli carried by the blood-stream has already been adduced. It is interesting to note that nearly all the subcutaneous nodules present were situated on the same side as the primary growth. This distribution is inconsistent with the embolic origin of these particular secondary growths, and strongly suggests a process of local spread, from point to point. On the other hand it is probable that most of the visceral deposits, perhaps those in the breasts, and a few of the subcutaneous nodules, took their origin in blood embolism. Such an embolic origin could be clearly traced in the kidneys, where the glomerular tufts were occupied in places by melanotic material, which at other points had burst into Bowman's capsule. Although "tissue-predisposition" is doubtless, as Mr. Stephen Paget showed, a factor in the survival of embolized fragments of growth, it is difficult to explain on these lines the relative freedom from metastases of the subcutaneous tissues of the left side, as compared with those of the right side.

As soon as the local spread in the lymphatics round the embolically invaded right femoral glands attained a radius of spread reaching to the level of the umbilicus—the dividing line between the territory of the inguinal and the axillary glands—embolic invasion of the axillary glands would occur. Local centrifugal spread around these glands, reaching a maximum in the rich lymphatic network of the breast, would account for the subcutaneous nodules present over the chest, and for the mammary masses of growth.

**Dissemination around a Primary Melanotic Sarcoma.**

Since in this case the primary growth had been removed by operation, it was not possible to study centrifugal lymphatic spread around the primary focus, but only around a secondary focus—the embolically invaded inguinal glands of the right side. And as these glands form the centre of important converging lymphatic trunks, it is probable that permeation might travel from them centrifugally with greater

rapidity than from a primary focus situated in a region more sparingly supplied with lymphatic communications. But for all practical purposes the conclusions arrived at from considering dissemination around an embolically-invaded gland, are applicable to dissemination around a primary growth, since wherever a focus of growth is situated it is in relation with the vast anastomotic network of fine vessels which lies at the periphery of the lymph-vascular system.

### **A Comparison between the Mode of Spread of Carcinoma and that of Melanotic Sarcoma.**

The principal aim of this research has been to test the conclusions on the spread of breast carcinoma at which I had previously arrived. For if it be granted that sarcoma can obtain access to and can exist within the lymphatic vessels, its mode of spread within them must be to a certain extent determined by the same mechanical factors as in the case of carcinoma, or of an artificial injection mass.

My conclusions on the spread of breast cancer were necessarily reached by microscopic methods only, but in melanotic sarcoma a direct appeal to the eye becomes possible; and Fig. 2 strengthens my former conclusions by indicating the identity of the mode of spread of melanotic sarcoma in the parietal tissues with the mode of spread which I inferred to take place in breast cancer.

In the earlier stages the processes of dissemination are essentially identical in carcinoma and in melanotic sarcoma. Dissemination is initiated by the access of malignant cells to the fine lymphatics, followed by the centrifugal spread of permeation along the main lymphatic plexus into which the primary growth pours its lymph, and by secondary permeation of small tributaries of this plexus. Embolic invasion of the regional lymphatic glands occurs, and around this fresh focus permeation recommences. Meanwhile, invariably in melanotic sarcoma and sometimes in carcinoma, invasion of the blood-stream takes place, either by local infiltration of veins from comitant permeated lymphatics, or by malignant cells carried into the blood along the thoracic duct from invaded lymphatic glands.



When this stage is reached dissemination in melanotic sarcoma and in carcinoma respectively, develops along divergent lines. In carcinoma lymphatic permeation, aided by the escape of cancer cells into the serous cavities, usually remains to the end the main agent in producing secondary growths—a fact which appears to depend upon the almost invariable destruction of such epithelial cells as obtain access to the blood-stream.

On the other hand the mesoblastic cells of melanotic sarcoma are frequently able to thrive when lodged in a blood vessel. Thus in the later stages of melanotic sarcoma the slow process of lymphatic permeation recedes into insignificance, and the patient dies with almost universal deposits resulting from blood-embolism—an event which as a rare exception may also occur in carcinoma.

#### IV.—THE OPERATIVE TREATMENT OF MELANOTIC SARCOMA.

At present the main principle followed in operations for melanotic sarcoma is to cut wide of the growth. For digital growths amputation is usually performed. For growths upon or near the trunk the usual procedure is, I believe, to enclose the growth at some distance by a fusiform incision passing directly down to the muscles, to dissect up the tissues enclosed by this incision from the muscles which lie beneath them, and to suture the edges of the incision.

The principles upon which, in my opinion, operation for melanotic sarcoma should be based may be directly deduced from Fig. 2. This drawing may be considered to represent a radial section of the parietes starting just at the edge of the growth and passing out into the surrounding tissues.

A circular incision should be made through the skin around the tumour at what is judged by present standards to be a safe and practicable distance. This incision should just be deep enough to expose the subcutaneous fat. If necessary, two radial linear incisions extending from the circular incision may be made on opposite sides of the tumour so as to facilitate the elevation of the skin-flaps, which forms the next step. The skin, with a thin attached layer of subcutaneous fat, is



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now to be separated from the deeper structures for at least two inches in all directions around the skin incision. At the extreme base of the elevated skin-flaps a ring incision down to the muscles surrounds and isolates the area of deep fascia and overlying deeper subcutaneous fat to be removed. This fascial area is next isolated centripetally from the muscles beneath, up to a line which corresponds with that of the circular skin incision. Finally the mass with the growth at its centre is removed by scooping out with the knife a circular area of the muscle subjacent to the growth. The edges of the wound are brought together as convenience dictates. The removal of the regional lymph glands is then proceeded with, and should in no case be omitted, for there can I think be no doubt that at a very early stage of the disease particles are swept to these glands by the lymph stream along the trunk lymphatic vessels.

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# A NOTE ON THE THERAPEUTIC MEASURES USED IN THE TREATMENT OF CARCINOMA IN THE CANCER WARDS DURING 1905.

BY WALTER BALL, M.B., B.S.

DURING 1905, as in former years, a number of the empirical methods which have been suggested for the treatment of cancer were investigated in the cancer wing of the hospital. No measure which was calculated to increase the pain or discomfort of the patient without holding out a hope of proportionate benefit was used.

Preliminary to the adoption of a method of treatment, the conditions under which it was being tried were fully explained to the patient and her consent obtained.

**I. Violet Leaves.**—The treatment of inoperable cases of carcinoma by the use of violet leaves was practised during 1903, without a beneficial result being noted.

In the spring of 1905 it was decided to give this form of treatment a further trial. For this purpose twelve patients suffering from cancer of various types, and in various stages, were selected, and subjected to a course of treatment lasting from one to six months.

The method of administration was as follows :—

By maceration of the leaves in boiling water, an extract was obtained, and pieces of lint soaked in this extract were applied to the diseased surface.

For uterine cases tampons saturated with the solution were passed into the vagina.

In addition a fresh infusion was prepared daily and one ounce and a half of it given three times a day by the mouth.

The results obtained are given in the subjoined table.  
All the patients treated were females.

Case.	Age.	Site of Growth.	Duration of Treatment.	Result.
I.	50	Uterus ... ..	5 months ...	Death, Nov., 1905.
II.	32	Uterus ... ..	6 months ...	Disease advancing.
III.	30	Uterus ... ..	2 months ...	Death, July, 1905.
IV.	40	Uterus ... ..	3 months ...	Death, July, 1905.
V.	48	Uterus ... ..	6 months ...	Discharged (no change).
VI.	37	Uterus ... ..	4 months ...	Death, Aug., 1905.
VII.	38	Uterus ... ..	1 month ...	Discharged (no change).
VIII.	69	Vulva ... ..	5½ months ...	Death, Sept., 1905.
IX.	63	Breast ... ..	4 months ...	Disease advancing.
X.	49	Breast ... ..	5 months ...	Death, Feb., 1906.
XI.	40	Breast ... ..	4½ months ...	Disease advancing.
XII.	63	Back of Neck (rodent cancer)	2 months ...	Disease advancing.

Thus of twelve cases subjected to a course of this treatment, two cases were discharged at their own request, their condition being unaltered, six cases died, and in the remaining four, which are still under observation, the disease is steadily pursuing its normal destructive course.

In no case was a beneficial result obtained, though temporarily the surface of ulcers cleaned as the result of the moist application.

**II. Betel Leaves.**—The claim to consideration of this method of treatment was based on the fact that in Java, the natives of which continuously chew the nut of the betel plant, cancer is said to be unknown. Three cases were submitted to this form of treatment, the betel leaves being chopped up fine, and applied directly to the diseased surface as a fomentation. The results obtained are shown in the subjoined table:—

Case.	Age.	Site of Growth.	Duration of Treatment.	Result.
I.	64	Breast ... ..	6 weeks ...	Death.
II.	55	Sternum ... ..	2 weeks ...	Disease progressing.
III.	45	Breast ... ..	6 weeks ...	Disease progressing.

Thus of three cases subjected to this form of treatment, one died and the remaining two failed to show any improvement.

III. **Uranium Salicylate.**—This substance, in the form of grain tabloids, was administered to a patient suffering from cancer of the breast three times a day for a period of six weeks. No beneficial result was obtained.

IV. **Caustic Paste.**—One case of carcinoma of the breast was treated by the local application of a plaster consisting chiefly of sulphate of zinc, but with other ingredients.

Its use was discontinued at the end of a month, the form and character of the growth remaining unaltered.

V. **Radium.**—The method of treatment carried out in this hospital consisted in the injection into the subcutaneous tissues of the patient of a liquid preparation of radium, made at the Chemical Laboratory of University College by Professor Sir William Ramsay, who will at a subsequent date publish a detailed account of the way in which it was obtained.

A small quantity of the fluid ( $1\frac{1}{2}$  cc.) was, with antiseptic precautions, slowly injected into the subcutaneous tissue of the abdominal or chest wall. Three cases were subjected to this form of treatment.

### CASE I.

Female, aged 45, suffering from cancer of the left breast. The left breast was entirely replaced by a large ulcerating mass of new growth.

Between 28th November, 1905, and 3rd February, 1906, the fluid was injected on seventeen occasions, the injections being made first into the subcutaneous tissues of the chest wall, and later into the abdominal wall. The last injection was made into the forearm.

Each injection was followed by a slight reddening of the skin at its site, and by a hard induration of the subcutaneous tissue.

The induration has persisted up to the present time.

After the fourth injection the surface of the ulcer showed signs of an increased formation of epithelium, which, however, soon disappeared.

No beneficial result was noted.



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A daily quantitative analysis of the nitrogenous and saline constituents of the urine failed to show any deviation from the normal.

### CASE II.

Female, aged 34, suffering from recurrent sarcoma of the thigh in amputation stump.

The maximum circumference of the stump at the commencement of the treatment was  $30\frac{1}{4}$  inches.

Between 27th November, 1905, and 3rd February, 1906, the fluid was injected on eighteen occasions, the injections being made first into the abdominal wall, and later into the chest wall.

Redness of the skin and induration of the subcutaneous tissues at the site followed. The induration still persists.

There was no evidence of any benefit from the injections, and the tumour increased in size.

Daily quantitative analysis of the urine showed no deviation from the normal.

### CASE III.

Female, aged 45, suffering from recurrent carcinoma of the right breast.

Between 8th December, 1905, and 25th January, 1906, the fluid was injected on thirteen occasions, the injections being made at first in the chest wall, and afterwards into the abdominal wall.

Each injection was followed by redness and induration as in the two previous cases.

The injections failed to produce any improvement in the patient's general or local condition, and on 8th February she died.

A post-mortem examination was not obtained.

Daily quantitative analysis of the urine showed no deviation from the normal.

A fourth patient on whom this form of treatment was commenced died after two injections from hæmorrhage in no way connected with the injections.

# THE HISTOLOGICAL DIAGNOSIS OF THE ENDOTHELIOMATA.

BY W. S. LAZARUS-BARLOW, M.D., F.R.C.P.

THE histological diagnosis of the endotheliomata is often so difficult, and the recognition of the entire group of neoplasms is so imperfect, that the results of an examination of all the microscopic sections that have been accumulated at the Middlesex Hospital during the past five years may not be out of place. These sections are about five thousand in number, comprising not only sections of the primary growth, but also sections of all metastases.

Although consideration has been given to the subject of endothelioma on the Continent, notably by Borst, the present paper is not a recapitulation of the views held by continental observers. On the contrary it will be seen that reasons are brought forward for believing that the group of the endotheliomata must be widened to include certain varieties of growth (occurring especially in the cervix uteri and the breast, but also occurring more rarely in other parts of the body) which are commonly, if not invariably, described as squamous or spheroidal cell carcinomata. The differentiation of the endotheliomata from certain forms of squamous cell carcinoma depends upon a further differentiation of the latter variety of growth. The view that it is necessary to sub-divide the squamous cell carcinoma was foreshadowed in these Archives (vol. iii, p. 81), and further investigations have fully confirmed the idea.

## **The Constitution of the Endotheliomata from a Theoretical Point of View.**

In order to obtain information as to the appearances which we should theoretically expect to find in the endotheliomata it is necessary to know the normal appearances of

endothelial cells. To obtain endothelial cells I cut a number of sections,  $1\mu$  in thickness, horizontal to the free surface of the pleura, and therefore obtained endothelial cells in their normal appearance and arrangement in the uppermost sections. In successful sections cells are seen, regularly arranged, flattened, with a large round or oval nucleus, and with a large amount of protoplasm to the cell. The nucleus of the cell has peculiar characters, which are not present, however, in every specimen. As a rule the chromatin is collected round the periphery of the nucleus, and also in the centre, while strands of chromatin extend between the two. Hence, in sections, the nucleus is remarkable by its clearness and its appearance of vacuolation. The protoplasm, as mentioned, is present in large quantity. These features are not so well seen in the guinea pig; in this animal the nucleus is more evenly stained, and there is a larger amount of chromatin. Moreover, the cells are not completely circular, but are polyhedral from mutual pressure. Nevertheless, it is characteristic of an endothelial cell to be round with a round or oval nucleus.

Since endothelial cells are found in special places, viz. the blood-vessels, the lymphatics and the lymphatic spaces, some idea may be formed of the types of growth that will result from their proliferation on theoretical grounds. The cells lining such spaces can proliferate either *inwards* or *outwards*, or in both directions at the same time. Outward proliferation will lead to production of a central space lined by endothelial cells, and surrounded by one, two or three layers of cells, more or less regularly arranged and with characteristic nuclei. The important point to note is that the central lumen will persist. If the proliferation of the endothelial cells take place inwards, the central space lined by endothelial cells will become filled with a mass of cells. According to these two hypothetical methods it should be possible to divide the endotheliomata into the "peritheliomata" and the "entheliomata." Further, if the perithelioma process occur in different situations, but in close contiguity, the effect will be that of a number of spaces, each more or less closely resembling the original space, but separated from one another by a mass of cells produced by the outward

proliferation and coalescence of the endothelial lining. On the other hand, in a growth of the enthelium type a number of cell masses will be seen corresponding to normal lymphatic spaces, in which the lumina have been distended and filled with cells, and which are separated by ordinary connective tissue. A combination of the two processes that have been described may occur, leading to a type of growth that may fairly be called a "perienthelium." \*

A convenient division of the endotheliomata is also into the "hæmal" and the "lymphatic." It is probable that the greater rapidity with which the blood flows through the blood-vessels and the higher hæmal tension militate against proliferation inwards, so that *a priori* enthelomatous growths should be more common in the case of lymphatics and peritheliomatous growths in the case of blood-vessels. It is difficult to say, however, in most cases where the growth originated, though sometimes the presence of red blood corpuscles in the lumina of a peritheliomatous growth renders it probable that a blood-vessel has become the seat of growth.

In the case of the lymphatics one is less sure, but certain peculiarities may lead to a suspicion that the case is one of lymphatic perithelioma. For the growth may show lumina containing a fairly circumscribed mass of albumin which has undergone coagulation in the process of fixation, and has given rise to fibrin and a certain amount of granular *débris*. This material represents, I think, the original lymph which circulated through a lymphatic which is now the seat of perithelioma.

*Diagnosis of Enthelium from Spheroidal Cell Carcinomas.*—In enthelium, if the cell masses of the growth are packed tightly together, the shape of the cells becomes polyhedral, and the general resemblance of a section to that of a spheroidal cell carcinoma is very great. In some cases the resemblance is to scirrhus, in others, to encephaloid carcinoma. But there is a fundamental difference between the arrangement of scirrhus and enthelium. For when the

\* To the best of my belief the two names "enthelium" and "perienthelium" have not hitherto been suggested for varieties of the endotheliomata, although they correspond well to varieties that are of constant occurrence.



enthelioma is spreading in distal portions of the lymphatics the cells become fewer and fewer as one passes outwards and become surrounded by inflammatory fibrous tissue, whereas in the centre of the tumour the growth is entirely cellular. In scirrhus of the breast the relative positions of the chiefly fibrous and the chiefly cellular portions of the growth are exactly reversed. The important practical point to be deduced from this is that it is necessary to know from what portion of the growth the section under consideration has been derived before a certain opinion can be given as to its nature.

*Diagnosis of Perithelioma from Angeiosarcoma.*—Great difficulties may present themselves in considering the relation of endotheliomata to the angeiosarcomata (hæmangeiosarcoma and lymphangeiosarcoma). I am convinced that the two conditions are independent.

If the term “endothelioma” is to be employed, it must signify a growth composed of endothelium without consideration of the tract from which it springs. Hence, if in a given growth there is not only that proliferation of endothelial cells which necessarily goes with a new formation of vessels, but *also an actual new formation of vessels*, the growth is a *complex vascular tumour*, and not a simple endothelioma. Bearing this point of distinction in mind it is usually easy to distinguish an angeiosarcoma from a pure perithelioma. In the case of the perientheliomata the matter is more difficult, for the cells of the latter often show a character different from the ordinary, and more of a sarcomatous type.

The lumina which constitute the characteristic feature of perithelioma are not always so well formed as in the normal blood capillary. Often in the hæmal peritheliomata and perientheliomata they are rather abortive attempts at forming tubes than real tubes, though they may contain blood. Nevertheless even these abortive tubes generally show a well-defined internal limiting membrane and are quite different from the blood spaces of the true sarcomata.

In other cases (viz. lymphatic peritheliomata) definite tubes are found lined, not by flattened endothelial cells, but by several layers of cells leaving a large central circular or oval space which may or may not be filled with débris. Reference is made to these cases later.

In the group of cases constituted by the perientheliomata and those other growths which are histologically so very similar to the perientheliomata but fundamentally are quite different, there are two appearances which often cause great difficulty, and the correct interpretation of which is of considerable importance. (1) Microscopic sections of a new growth may show masses of cells many of which contain a central small "core" composed entirely of connective tissue. (2) A condition obtains in which the appearances are very similar at the first glance, but the central "core" consists peripherally of either round or oval nuclei with sharp outlines, and in the centre of a single layer of cells with elongated, deeply staining nuclei, and resembling the flattened endothelial cells lining a normal vessel; further, all these cells surround a contracted central lumen. In a description it seems impossible to confuse the two appearances, but since the "core" in each case is generally separated from the surrounding cell mass and itself appears to lie in a lumen, it is frequently difficult to decide whether the "core" represents fibrous tissue forming a portion of the stroma or a space with an endothelial lining in the centre of a mass of perithelioma. The point is important because in a group of cases of squamous cell carcinoma, to which reference will be made later, the appearance described under (1) is common.

In many malignant tumours of the breast and uterus the growth consists of large masses of cells arranged round a central débris. It is usually considered that these are cases of spheroidal or squamous cell carcinoma which have undergone necrosis in the centre of the cell masses. But the appearances in the cases under consideration differ fundamentally from cases in which it is indubitable that solid masses of cells have undergone central degeneration. In the case of a solid mass of cells the central portion of which is undergoing degeneration a transition between the fully normal and the fully degenerated cells is recognisable. But in these cases the appearances are different. For every single tumour cell of this group of cases is as well formed as its fellows, there is no "shading off" from the well-formed peripheral cells to the central degenerated material. Moreover a definite layer of flattened cells, exactly like that which constitutes

the ordinary endothelial lining of a vessel, may lie next to the central débris. I believe that these cases so frequently called squamous cell carcinoma when implicating the cervix and spheroidal cell carcinoma when implicating the breast, are in reality lymphatic peritheliomata, and that the central material is as often an organising as a degenerating thrombus in a dilated lymphatic channel. Frequently polymorphonuclear leucocytes are present in this central material.

*Diagnosis of Endotheliomata from certain varieties of Squamous Cell Carcinoma.*—In common practice the diagnosis of "squamous cell carcinoma" of the uterus, lip, mouth, etc. really depends upon the discovery of cell nests. In the absence of cell nests it is often very difficult to distinguish squamous cell carcinoma from other types of growth, especially if we do not allow ourselves to be biassed by a knowledge of the site from which the primary growth was taken.

From a theoretical point of view it is possible to obtain at least five different kinds of growth—all of them squamous cell carcinomata—from the normal layers of the epidermis. These varieties are (1) a growth of pure Malpighian cells; (2) one of Malpighian and prickle cells; (3) one containing Malpighian cells, prickle cells, and keratinising cells. All of these may be derived from a point involving the Malpighian layer alone. Arising from the prickle cell layer might be produced (4) a pure prickle cell carcinoma, and (5) one composed of prickle cell and keratinising layers. A pure keratinising squamous cell carcinoma probably does not exist, but examples of the five varieties which have been given are common. Further a pure Malpighian squamous cell carcinoma maintains its characters so that in its metastases prickle cells and keratinising cells (cell nests) are absent. Within limits, the same is true for the pure prickle cell carcinoma. Consequently diagnosis of the squamous cell carcinomata from the discovery of cell nests becomes far too narrow.\*

\*The case is further complicated by the fact that many authors have described the occurrence of cell nests in the endotheliomata. There is no inherent reason why appearances similar to those which we call "cell nests" should not be formed in the endotheliomata. Nevertheless I have never found a cell nest in an endothelioma with which I have been really satisfied. This difficulty is, however, a relatively small one.



The following suggestions may be of use in framing a diagnosis between a pure Malpighian cell carcinoma, a pure prickle cell carcinoma, and an endothelioma.

The Malpighian cell is normally a large cell with a deeply staining nucleus which is almost always oval or elongated. The prickle cell is much larger, has a central nucleus, which may or may not stain deeply, but which has the peculiarity of standing away from the cell protoplasm so that it lies, or appears to lie, in a clear space in the centre of the cell.

Now it is evident that when endothelial cells are proliferating rapidly they tend to resemble Malpighian cells, and when proliferating at a slow rate they rather resemble prickle cells, with the production of neoplasms histologically resembling the Malpighian and the prickle cell type of carcinoma respectively. I am accustomed to differentiate between these squamous carcinomata and the endotheliomata by examining for the space normally present between the prickle cells. I believe that these prickle spaces are always present in a squamous cell carcinoma even if it be of the pure Malpighian type.

With regard to carcinoma of the Malpighian type there is no lack of examples. They show a tendency to close packing of their cells while the nucleus takes a deep stain and the cells themselves are prone to be more spindle-shaped than oval. On the other hand the endotheliomata are characterised by the peculiar brilliancy of the histological sections made from them. The reason of this difference in brilliancy lies in the fact that in carcinoma the cells are more tightly packed and the cell body forms a smaller proportion of the entire cell; hence light is not so readily transmitted through the section. The prickle cell variety of carcinoma is an exception, as might be expected, and gives sections as brilliant as the endotheliomata, though it differs from the latter in other respects.

With regard to the frequency with which endotheliomata are met, the following table gives the results of an examination of most of the histological material accumulated at the Middlesex Hospital during the past five years. Some of the organs and tissues in which primary new growths occur are not mentioned in the table because it has not been possible,



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so far, to work the matter out. It is necessary to add that the diagnosis has been my own in all cases, whether of endothelioma or of other variety of malignant disease. This remark is necessary since it is certain that in a group such as is now under discussion other pathologists might hold different opinions on some of the growths. The main point in their favour is that it is probable that the figures have a relative if not a positive value owing to their having been compiled by one worker.

*Table showing the number of cases histologically diagnosed as Endothelioma at the Middlesex Hospital during the years 1900-4 :-*

	Total cases of Malignant Disease.	Cases of Endothelioma.
Lip ... ..	50	0
Tongue ... ..	80	6
Mouth, palate, cheek ... ..	21	0
Esophagus ... ..	32	0
Stomach ... ..	54	0
Uterus, vagina, vulva ... ..	175	17
Breast ... ..	300	32
Liver and bile passages... ..	10	1
Bones, antrum, upper jaw ... ..	44	3

From this table it appears that endothelioma constituted 8 per cent. of the malignant diseases of the tongue, 10 per cent. of the uterus, 10 per cent. of the breast, 10 per cent. of the liver and bile passages, and 7 per cent. of the malignant diseases primarily affecting bones.

In comparing the microscopic slides with the records of the patients it was noticed that cases histologically diagnosed as "endothelioma" showed an abnormally large number of metastases. Of the seventeen cases of endothelioma of the uterus fourteen were associated with numerous and wide-spread metastases. This percentage (82 per cent.) is far higher than obtains for malignant disease of the uterus generally. In the case of the breast only five autopsies have been made in the past five years in which the case proved to be endothelioma (operation cases are clearly excluded when considering wide-spread metastases). One of these had metastases in the axillary glands only, but all the others showed

enormously wide-spread metastases. The number of metastases associated with a growth may therefore help us in forming a diagnosis when its histological characters are uncertain. Like the other criteria, however, that have been mentioned, it must not be taken alone or given undue weight. This caution is the more necessary since on the Continent many innocent parotid tumours are considered to be endotheliomata and certainly endotheliomata of the cerebral dura mater are not malignant in the sense of forming metastases.

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# ON CHORIONEPITHELIOMA OF CONGENITAL ORIGIN.

BY VICTOR BONNEY, M.S., M.D., B.Sc. (LOND.), F.R.C.S.,  
M.R.C.P.

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BY the kindness of Dr. Karl Fürth I have been permitted to publish the following case:—

F. R. aged 69 years, a bootmaker, was admitted into the German Hospital, Dalston, on the 12th September 1905. He had been quite well until eight weeks previously, when he noticed slight swelling of his ankles. This extended upwards to his legs; later the abdomen became enlarged. He lost appetite and flesh, but had been at work until his entrance into the hospital.

On admission he was thin and cachectic in appearance, and had marked oedema of both legs. The heart and lungs were normal. There was considerable ascites, and marked distension of the superficial abdominal veins.

In the middle line between the pubes and umbilicus was situated a hard mass, somewhat ill-defined on account of the ascites. It was not painful, but the patient complained of a distressing sensation of fulness and distension. The urine and stools were normal.

On September 14th, the stomach tube was passed and the contents of that viscus examined. No free hydrochloric acid was present, and there was an absence of lactic acid and

bacteria. On September 21st, the peritoneal cavity was tapped and 4,000 cc. of sanguinolent fluid was withdrawn. The same afternoon the patient died.

At the autopsy the following condition was found :—

The abdomen was full of sanguinolent fluid. Immediately underneath the anterior abdominal wall, and apparently situated in the great omentum, was a tumour the size of a man's head, of lobulated shape, of a deep red colour, and of soft consistency. On section it was solid throughout and presented a number of hæmorrhagic areas interspersed amongst others of a pale pink or buff colour. Above, it was adherent to the greater curvature of the stomach, and elsewhere it was surrounded by many adhesions.

The liver was considerably enlarged, nodulated, and contained a number of metastases which varied in size from a pea to an orange. These growths externally were of a deep red colour. Their appearance on section (Plate I) resembled in a striking manner the naked-eye appearance of a chorion-epithelioma.

No other secondary growths were found. The other organs of the body were normal. Both testes were incised, but no pathological appearances were present.

Portions of the primary tumour were removed for microscopical investigation, and a large piece of the liver was preserved in Kaiserling's solution. Unfortunately the bulk of the primary tumour was not kept. The tissues reserved for microscopical examination were fixed in formalin, embedded in paraffin, and the preparations were stained by hæmatoxylin and eosin. These preparations were closely investigated at the Cancer Research Laboratories of the Middlesex Hospital, when it was recognised that the tumour bore a striking resemblance, not only macroscopically, but microscopically to chorionepithelioma. The details of the microscopic appearances will be referred to later (p. 92).

## ON THE OCCURRENCE OF CHORIONEPITHELIOMATOUS GROWTHS APART FROM PREGNANCY.

Since the publication of Teacher's monograph on chorion-epithelioma (1) it is generally accepted, here, as on the



Continent, that these neoplasms when associated with pregnancy arise from the non-foetal portion of the embryonic ectoderm or "trophoblast" (Hubrecht).

Within the last few years, however, tumours simulating chorionepithelioma have been described not only in women in the absence of pregnancy, but also in men. By far the greater number of these have arisen in pre-existing teratomata. The credit of the suggestion that these tumours are really chorionepitheliomata arising from chorionic elements present in the teratoma, is due to Schlagenhauser (4); subsequently, Pick (5-9), working, not only independently, but on material derived from quite different sources, confirmed his views.

The acceptance of this view must be based on the proof of two propositions:—

1. That the histological features of the group of tumours under consideration are identical with those of chorionepithelioma.

2. That they arise from cells ontogenetically identical with those of the trophic ectoderm of the embryo.

### THE HISTOLOGY OF CHORIONEPITHELIOMA.

A short recapitulation of the histology of chorionepithelioma is necessary in order that the class of tumours with which this paper is concerned may be compared with them.

Macroscopically, chorionepitheliomata present a dark red colour, and the larger masses have frequently a lobulated outline. On section their appearance is quite characteristic, the peripheral parts of the tumour presenting a number of dark red hæmorrhagic areas interspersed with smaller cream-coloured patches. Centrally, the tumour usually consists of necrotic cell elements, decolourised blood clot and fibrin.

Microscopically they contain three types of cells, without intercellular stroma, but lying in irregular masses in or between areas of fibrin and blood clot.

These types are as follows:—

- (1) *Hyaline Cells*.—Small closely-packed polyhedral cells with a singularly transparent cytoplasm and a rounded nucleus which exhibits a loose chromatic network. These cells are usually arranged in masses, having a somewhat

festooned outline, and are not found isolated amongst the fibrin elements, or invading singly the pre-existing tissues.

(2) *Syncytial Masses.* Large syncytial masses containing many nuclei, some of which are small and stain deeply, others are much larger, lobulated or reniform in outline, show a distinct chromatic network, and are usually vacuolated. Syncytial masses vary enormously in size. Some are very large with irregularly pointed processes, whilst others are thin and elongated, and the nuclei contained within them compressed and flat. The latter form is most commonly observed, bounding the festooned masses of hyaline cells already described. Syncytia are usually found on the surface of a blood-containing space.

(3) *Large Mononuclear Cells.*—Large irregular mononucleated cells of varying character which appear to originate from both the hyaline polyhedral cells and the syncytial masses. In the first case the cytoplasm of the small hyaline cell appears to increase in size owing to the deposit in it of granules of glycogen whilst the nucleus becomes larger, ovate, and increasingly chromatic. The tessellated appearance of the cell mass remains, however, and indicates its origin. When originating from syncytia the cells can be distinguished from the preceding group by their isolation, by their very large, irregular, vacuolated nuclei and by their homogeneous non-granular cytoplasm. They are found embedded in masses of fibrin or blood clot.

The author, in conjunction with Comyns Berkeley, (3) published the results of an investigation into the histology of early tubal gestation, and we have no hesitation in saying that all the cell forms just described can be seen in the wall of an early extra-uterine gestation-sac. The small hyaline cells are identical with the "Langhans" cells of the chorionic villus, the syncytial masses are identical both in position and character with those bounding the periphery of the intervillous blood spaces, whilst the mononuclear cells are identical with the large cells invading the tubal muscle or embedded in the fibrin masses. (Plate II., Fig. 1.)

But whilst the general cell features described are common to all these tumours, there exist between individual specimens great differences as to the proportions in which these varying

cell types are found. These various forms have been especially studied by Marchand (2) who divides the chorionepitheliomata into typical and atypical varieties. Thus tumours have been described consisting almost entirely of the young hyaline "Langhans" cell ("Langhanseoma") others again are almost entirely made up of syncytium ("Syncytioma Malignum"). The *young* hyaline "Langhans" cell (vide Plate II, Figs. 1 and 2), is perhaps the rarest cell type in these growths. More commonly the predominant form is the large mononuclear cell already described as originating from the "Langhans" cell by hypertrophy and accumulation of glycogen and chromatin. In some tumours, or in certain parts of the same tumour, the second type of large mononuclear cell, namely that derived from the breaking up of the syncytial mass, is most noticeable. The present case is of this type.

On Plates III and IV, the histological characters distinguishing two different types of uterine chorionepitheliomata are shown.

Besides the pure chorionepitheliomata, tumours are known which bridge the gap between them and the vesicular moles. Such tumours possess, not only elements derived from the trophic ectoderm, but also the whole structure of villi in a state of vesicular degeneration, and consequently they may be rightly termed "choriomata." At the other end of the series are the vesicular moles proper which exhibit various degrees of invasional activity ranging between malignancy and innocency.

## ON THE HISTOLOGICAL IDENTITY OF CERTAIN TUMOURS ORIGINATING APART FROM PREGNANCY WITH RECOGNISED CHORIONEPITHELIOMA.

### A.—The Author's Case.

The primary tumour presents a well marked capsule of fibro-cellular tissue, infiltrated in many parts with blood, and covered on its external surface by a layer of endothelium. Immediately against the capsule are masses of cells which present a sharply defined growing edge. These masses are

arranged in an irregular manner, being partially separated from one another by aggregations of blood or strands of fibrin, containing leucocytes, which often penetrate between the individual cells.

In a few places prolongations inwards of the capsule are visible, but except for these no intercellular stroma is present.

As the central portions of the tumour are approached the aggregations of blood and fibrin become larger, and the groups of cells more scattered. Deeper still, marked evidence of necrosis is seen, the areas of the blood clot becoming decolourised and structureless, fibrin masses predominant, and the tumour cells pale and indistinct.

The cell elements of the growth are of three distinct types.

(a) Immediately under the capsule is a track of small hyaline cells, massed together in a "tessellated" manner, and exhibiting a vesicular nucleus with a distinct chromatic network. These cells are thrown into festoon-like masses. (Plate II, Fig. 3.)

(b) Large irregular syncytia of very variable shape. They are seen bounding the festooned masses of hyaline cells and dipping down between them as thin processes. Here they are very narrow, and resemble an endothelium. In other parts they run in towards the capsule in a series of elongated flame-like strands. Elsewhere they present irregular shapes, with fine pointed processes extending out amongst the other cell elements. Their nuclei vary greatly, being elongated, flattened and deeply chromatic in the narrow strands, but lobulate, pale and vacuolated in the larger masses.

(c) Irregular cells exhibiting all gradations in size and shape between the hyaline cells and the syncytia. In some parts they obviously originate by syncytial disintegration, but in others exhibit continuity with the small hyaline cells. In general their shape is irregular, their cytoplasm chromatic, and their nuclei large and variable in appearance. Thus these may be vesicular, deeply chromatic, or vacuolated, and in shape round, oval, or lobulate. Not infrequently giant nuclei are observable, whilst in some cells the nucleus is divided into two halves by a thin transparent line.

In the central portions of the tumour these cells become more isolated amongst the masses of fibrin.



Leucocytes are sparsely seen at the growing edge, but are present in great quantity in the central parts of the tumour amongst the masses of fibrin and blood clot. In the necrotic areas they appear to have remained intact longer than the other elements, their nuclei standing out amidst the general pallor.

The metastases in the liver present the same general appearance. (Plate V.) The growing edge is well defined, the liver cells in this situation are compressed, and there is a complete absence of any reaction to the tumour cells, which resemble those of the primary growth, except that the small hyaline cell is nowhere observable. Especially noticeable are certain large spaces, whose walls are bounded, either by syncytia or by very large mononuclear cells with giant nuclei. These spaces contain unaltered blood.

The peripheral parts of the metastases exhibit large intercellular extravasations of blood, but centrally they are necrotic like the primary tumour.

#### **B.—The Previously Recorded Cases.**

These may be grouped under three heads according as the primary growth was in (I) the testicle, (II) the ovary, or (III) other situations.

##### *I.—Cases Primary in the Testicle.*

1. Waldeyer (10) under the name of "Myxoma intravasculare" described a tumour of the testicle containing cystic spaces with islands of myxomatous tissue and cartilage from which outgrowths invaded the spermatic veins. These outgrowths were "only comparable with the villi of vesicular mole."

2. Kanthack and Pigg (11) described an almost similar case with metastases in the prevertebral glands, liver, inferior vena cava, and right auricle. The description of the metastases in glands, liver, and vena cava strongly suggests secondary teratomatous growths containing chorionepitheliomatous tissue. From the tricuspid valve projected a branched mass resembling externally, as in Waldeyer's case, a vesicular mole.

3. Macallum (12) described and illustrated a remarkable case in which the testicular tumour is described as myxomatous,

hæmorrhagic, and partly necrotic. The inferior vena cava, right auricle, pulmonary vessels, jugular and subclavian veins, and some of the cerebral sinuses were filled with a growth, macroscopically and microscopically, "resembling nothing so much as a hydatidiform mole."

4. Silberstein (13) recorded an almost similar case. The primary tumour was complex and suggested a teratoma. The pulmonary metastases from the description may be chorion-epithelioma, whilst in the right auricle was a hydatidiform mass.

5. In 1903 Schlagenhauser first stated that the occurrence of chorionepitheliomatous and vesicular mole-like structures in the absence of pregnancy was to be explained by attributing their origin to elements of the trophic ectoderm or of the chorion occurring in teratomata. He published two cases in support of his contention.

The first was a specimen originally described by Breus. The primary tumour in the testicle was an undoubted teratoma containing entire villi in a state of vesicular degeneration. In the lungs were secondary growths identical with chorionepithelioma and embolic areas containing villus-like plugs. In the left auricle was a mass exactly resembling a vesicular mole.

The second case was somewhat different, the metastases in the lungs presenting a chorionepitheliomatous structure only. The primary tumour in the testicle was a teratoma containing elements derived from all the three layers of a trilaminar blastocyst. (Plate VI.)

6. Steinhaus (14) has recorded a case identical with Schlagenhauser's second case.

7. In 1896 Kanthack and Eden (15) showed a specimen identical in structure with "deciduoma malignum," but derived from the testicle.

8. Wlassau (16) investigated the "sarcome angioplastique" of certain French authors (17-18-19). He pointed out that all the described cases had originated in the testicle and added four cases of his own. He noted the resemblances to chorion-epithelioma, but considered that the malignant cells originated from the imperfectly differentiated epithelium of the embryonic gland tubes. The stromal portions of the

testicular growth, however, he recognised as arising from an embryonic inclusion.

9. Steinert (20) investigated a rapidly growing tumour of the testicle (Schmorl's case). Secondary growths were present in the retro-peritoneal lymph glands and formed a mass the size of a head. Smaller metastases were present in the liver. The primary tumour was a typical teratoma, representatives of all the three primitive layers being present. In one small part of the mass was found an area of typical chorionepitheliomatous structure. The metastases in the retro-peritoneal tissue were also teratomatous. In addition certain large spaces lined by a cylindrical epithelium were present which showed marked proliferation of a carcinomatous type. In other parts typical "Langhans" cells and broken up syncytia were found.

In the liver the growth consisted of syncytial masses and of the large irregular cells derived from syncytial disintegration.

10. Emanuel's case (21) is of the same character as that of Steinert. The tumour situated in the testicle caused death in three months, with metastases in the right lung, liver, retro-peritoneal glands, and pancreas, which macroscopically resembled chorionepithelioma. The retro-peritoneal mass was of great size. Microscopically, *both in the primary and secondary tumours*, was found a tissue consisting in parts of tubular spaces lined by epithelial cells resembling carcinoma, and in parts of typical chorionepithelioma, whilst besides these were found simple cysts lined by a cylindrical epithelium. He considered the case to be one of simultaneous carcinomatous and chorionepitheliomatous degeneration of a teratoma, and believed both types of growth to have been derived from embryonic ectoderm.

11. v. Hansemann (22) has reported a somewhat similar case. The testicular growth and the metastases in the liver, spleen, and the bulk of the retro-peritoneal glands showed a chorionepitheliomatous structure only. In some of the lower glandular metastases, however, spaces lined by cubical or cylindrical epithelium were found. The tumour was held to be of teratomatous origin on account of the cystic spaces found in the metastases.

12. Dillman (23) has published a case of particular interest. The patient died of a very large retro-peritoneal tumour of a bluish-red colour with other smaller masses in the lung. All these growths showed a typical chorionepitheliomatous structure. The left testicle was normal in size. Near the hilus was a whitish mass the size of a cherry, composed of connective tissues containing cystic spaces, the epithelium of which appeared to be proliferating to form masses of "Langhans" cells, having a carcinomatous arrangement.

13. Risel (24) has investigated two specimens. In the first the primary tumour presented not only chorionepitheliomatous tissue but also appearances suggestive of a proliferation of neuro-epithelial structures. He regarded the specimen as arising from embryonic ectoderm.

In his second case the testicle had been previously removed, and was not available for examination. Post mortem the metastases in the retro-peritoneal tissue, inferior vena cava, fourth lumbar vertebra, lungs, and liver exhibited a typical chorionepitheliomatous structure. In addition portions of the retro-peritoneal mass showed duct-like spaces, lined by small cubical cells which Risel suggested were derived from the epithelium of the seminiferous tubules or from epithelial tissues present in the primary tumour.

14. Askanazy (25) has interpreted cases such as Risel records in another manner. He has himself investigated a primary chorionepitheliomatous tumour of the testicle, and asserts that the "Langhans" cells or their prototypes in the teratoma may at times assume atypical arrangement of a tubular or alveolar character.

15. Scott and Longcope (26) have described a specimen in an undescended testicle; it contained no teratomatous tissue, but only cells of the "Langhans" type. The metastases were typical.

16. Frank (27) has described two specimens. In the first the general arrangement was alveolar with papillary projections resembling villi, no teratomatous structures were present. The second case was held to be a teratoma containing chorionepitheliomatous tissue. The subsequent history of these two cases, both of which were operated on, is unknown.



*II.—Cases Primary in the Ovary.*

In this group are considered 7 cases reported by L. Pick, and 3 cases reported by Michel, by Schmaus and by Kleinhaus.

1. Pick's cases (5-9). The earliest published case was that of a woman from whom the right adnexa were removed for tubal gestation. The ovary contained a "dermoid" cyst with hair, teeth and bone (teratoma), but towards its uterine pole was another smaller cyst containing clear fluid, in which was found a mass resembling both macroscopically and microscopically a vesicular mole. Although the possibility that this represented a metastasis from the tubal gestation could not be excluded, Pick considered that the balance of probability favoured the view that it was a primary development from an ovarian teratoma.

His second case was that of a girl, 9 years old. Microscopically the growth contained teratomatous structures from which were proliferating a typical chorionepitheliomatous growth, together with tissue of a neuro-epithelial character.

Subsequently Pick investigated five similar cases, the details of which need not be repeated.

2. Michel's case (28) was an undoubted virgin of 16 years. A dark red tumour was removed from the left ovary, together with a pedunculated metastasis from the back of the left broad ligament. The patient died later with a large recurrence in the lower abdomen, and numerous smaller masses in the kidneys and liver. These presented to the naked eye the appearances of a chorionepithelioma. Microscopically in the paler parts of the large mass were groups of hyaline polyhedral cells surrounded by a spindle-celled stroma. In the hæmorrhagic areas large syncytia were seen together with many large mononuclear cells. The general arrangement of the hyaline cell masses was carcinomatous, but they showed the festoon-like appearance of the "Langhans" cell masses in chorionepithelioma. The growths in the liver and kidneys presented only the syncytia and the large mononuclear cells.

Michel regarded the case as one of carcinoma of the ovary of a chorionepitheliomatous type, but Pick subsequently criticised this conclusion and declared the case a chorionepithelioma

arising in a teratoma. (Central. für Gynaec. 1905. No. 18-26.)

3. Schmaus (29) has reported a case which he describes as an adenocarcinoma of the ovary with chorionepitheliomatous metastases in the peritoneum. A perusal of the description leaves one unconvinced as to the exact character of the secondary growths. Pick, however, believes this case also to be a chorionepithelioma.

4. Kleinhaus' case (30) was that of a woman who was operated on for supposed tubal pregnancy. The tube was normal, but there was a hæmorrhagic tumour of the left ovary which was chorionepitheliomatous in structure.

The patient subsequently died and post mortem were found chorionepitheliomatous metastases in the lungs and vagina. Kleinhaus, who published the case at a period antecedent to Schlagenhauser's paper, considered that the growth arose from an ovarian gestation. The case must be considered doubtful.

### III.—*Tumours Primary in Situations other than the Testicle and Ovary.*

1. Bock's case (31) was that of a girl 12 years old, almost certainly a virgin, who at her fourth monthly period passed per vaginam a typical vesicular mole.

2. In Lubarsch's case (32) a large uterine tumour of typical chorionepitheliomatous appearance and structure was removed from the uterus of a virgin aged 12 years.

3. Boström's case (33). In this case a small intracranial tumour, having a typical chorionepitheliomatous structure, was removed from a man aged 30 years. The patient died shortly afterwards and a large retro-peritoneal tumour was found, with smaller growths in the lungs, liver, and kidneys, all of which, both to the naked eye and under the microscope, were identical with a chorionepithelioma. The testes were normal.

4. Djewitzki (34) has recorded the case of a virgin 75 years of age, in whom was found a chorionepitheliomatous growth of the posterior surface of the bladder, with secondary growths in the lungs, bronchial glands, spleen, and sigmoid flexure. No teratomatous structures were found.

5. Ritchie (35) reported the case of a man in whom a large tumour occupying the anterior mediastinum was found, which consisted of (a) an area presenting the typical structure of a teratoma containing skin, sebaceous material, hair, etc. and (b) a solid portion macroscopically and microscopically identical with a chorionepithelioma. In the lungs were many nodules, typically chorionepitheliomatous. (Plate VII.)

6. Frank (27) lately reported a case in which post mortem a mediastinal tumour was found in a young man, together with metastases in the lungs and liver, all presenting a typical chorionepitheliomatous appearance and structure. No evidence of a teratoma was found, but the case unfortunately could not be thoroughly investigated.

7. Marx (36) has reported a primary tumour of the liver which microscopically resembled a chorionepithelioma.

A study of the foregoing cases, therefore, reveals a remarkable histological identity between the class of tumours under discussion and the chorionepitheliomata, vesicular moles and mixed tumours (choriomata) occurring in connection with pregnancy. We see also in these tumours the same tendency to depart from the typical cell characteristics which we have already remarked in the chorionepitheliomata. In short the typical and atypical forms of chorionepithelioma, described by Marchand, are reproduced in these cases.

The chorionepitheliomatous nature of these tumours of the testis, ovary, and certain other situations is, however, not accepted by all observers. Certain workers regard them as a form of carcinoma. The views of Wlassau, of Michel, and of Schmaus have already been indicated when describing their cases. Foulerton (37) believes that appearances such as those described by Schlagenhauser may be present in what he regards as undoubted columnar cell carcinoma of the testis. Finally Sternberg (38) has combated Schlagenhauser's views, and whilst considering a case of his own as a perithelioma, holds that many tumours, both carcinomatous and sarcomatous, may at times take on a syncytial form.

Consideration of these views may be postponed until the evidence in favour of an inclusional origin of these tumours has been adduced.

ON THE ONTOGENETIC IDENTITY OF CERTAIN  
TUMOURS ORIGINATING APART FROM  
PREGNANCY AND RECOGNISED  
CHORIONEPITHELIOMA.

The absolute identity of the tumours under discussion with chorionepitheliomata, chorioma, and vesicular mole cannot be proved by their histological resemblance. Such a view, however, is greatly strengthened, if it can be shown that it is reasonable to suppose that they arise from cells ontogenetically identical with elements of a trophoblast or chorion. There is no doubt that the majority of chorionepitheliomata originating in the absence of pregnancy have arisen *in connection with teratomata*. In the following paragraphs it will be shown that there is reason for believing that they may actually constitute the entire teratoma themselves.

We do not propose to discuss the possibility that a teratoma can originate from the inclusion of one ovum within another at any period of its existence, for we regard such an occurrence as in the highest degree problematical. With this exception it is possible that teratomata arise from :—

1. A single undifferentiated blastomere, or an equivalent cell.
2. The layers of the blastocyst.
3. Specialized derivatives of any one of the layers of the blastocyst.

**A.—Blastomeric Inclusions.**

Owing to its potentialities the undifferentiated blastomere, or any cell equivalent to it, may be regarded as capable of producing all varieties of teratoma. For even those composed of elements derived from only two or one layer of the differentiated blastocyst, may be explained on the assumption that the sequestered blastomere, or equivalent of a blastomere, does not necessarily produce all the three layers when it eventually develops, or that it may produce elements of one layer in such excess as to obscure the others. Pick (6) has emphasized the last possibility and pointed out that the ovarian tumours



first described by him as *Struma Ovarii* could by serial sections be proved to be teratomata in which thyroid tissue had developed to such a degree as to almost conceal the other elements.\*

### B.—Inclusion from the Layers of the Blastocyst.

Upon this view the teratomata have been formed from inclusion occurring after the primitive layers have been formed (bilaminar or trilaminar blastocyst). Thus an ectodermic inclusion developing at a later date might (theoretically) form trophoblast tissue, squamous and columnar epithelium and nerve elements. (Cf. the direct association of chorio-epithelial and neuro-epithelial tissues in teratomata as described by Pick and by Risel.)

### C.—Inclusion from Specialized Derivatives of Layers of the Blastocyst.

Inclusions may take place after the differentiation of the primitive layers into their permanent derivatives (e.g. facial dermoids), the tumours formed as a result of such inclusions presenting a simpler type than the foregoing. The possibility, therefore, of an inclusion of trophoblast cells in the embryo cannot be denied.

It is thus evident that the chorionepitheliomata may theoretically not only arise as part of an inclusional tumour, but may constitute the entire inclusional tumour itself.

In explanation of the frequency with which teratomata affect the ovary and testicle, I would suggest :—

1. That the cells of the germinal epithelium and all their derivatives should be considered as normal sequestrations of elements of the undifferentiated blastocyst ;
- and
2. That these cells have on occasion the power of proliferating in the absence of sexual fusion.†

Turning now to the view that these tumours are really carcinomata it is noteworthy that most of the recorded testi-

\* An interesting confirmation of this observation will be found in the Trans. of the Obstet. Soc. London, 1905, pp. 242 and 297.,

† Professor Arthur Robinson has shewn me slides of the rat's ovary, exhibiting asexual division of the ovum in the follicle. He tells me that it is not an uncommon occurrence in this animal.

cular cases have certainly arisen in the mediastinum testis. The explanation of such cases as "carcinomata" depends upon the tacit assumption that the epithelium-lined spaces of the growth represent tubules of the mediastinum testis. It is by no means certain, however, that the cells lining the tubular spaces of the mediastinum testis constitute an ordinary differentiated epithelium, such as is usually regarded as capable of originating a recognised carcinoma; embryologically, their origin is uncertain. The great diversity of testicular growths certainly seems to suggest that they represent a far more primitive, and therefore less differentiated, type of cell.\*

In the case of ovarian growths which contain epithelium the argument is even stronger, since no portion of the normal ovary is regarded at the present time as being of ectodermic origin.

Nor is the fact that these spaces at times re-appear in the metastases an argument for their carcinomatous nature. For when a teratoma becomes malignant, that malignancy may show itself in virtue of any one element or combination of elements contained within the tumour. Thus in two cases published by Targett and Hicks (39) the multiform structures characterising the primary growth were faithfully reproduced in all the metastases.

And finally the continuity which can be traced in some of these tumours between cells indistinguishable from trophoblast and various types of epithelium is most easily interpreted on the assumption that the growths originate from primitive undifferentiated cells.

*Note.*—I have to tender my thanks to the following gentlemen for giving me microscope slides of their specimens of chorionepithelioma:—Professors Schlagenhauer, v. Hanse-mann, and Pick; Messrs. Teacher, Ritchie, Risel, Hicks, Maynard Smith, and Spillsbury. To Dr. E. Schenck I am indebted for collecting the literature.

\* Bland-Sutton has suggested that the testicular "dermoids" may possibly originate in ovarian elements sequestered in the mediastinum testis. Archives of the Middlesex Hospital, vol. i. p. 19.

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## DESCRIPTION OF PLATES.

### PLATE I.

*The Author's Case.*—Macroscopic appearance of a section across one of the metastases in the liver.

### PLATE II.

FIG. 1.—A portion of the wall of an early tubal gestation-sac, showing syncytia bounding the intervillous blood space, large mononuclear cells invading the tubal muscle, which has undergone fibrinoid degeneration, and a small group of young hyaline "Langhans" cells. Obj. 1 inch. Ocular No. 8. Camera Lucida.



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FIG. 2.—A chorionic villus from an early vesicular mole showing proliferation of young "Langhans" cells. (From a slide of Dr. John Teacher's.) Obj. 1 inch. Ocular No. 8. Camera Lucida.

FIG. 3.—*The Author's Case*.—A portion of the primary tumour. Immediately under the capsule are seen festooned masses of small cells, with hyaline cytoplasm and round vesicular nuclei. They are bounded on their further surface by delicate syncytial strands simulating an endothelium. Obj. 1 inch. Ocular No. 8. Camera Lucida.

### PLATE III.

Section of chorionepithelioma of the uterus associated with pregnancy. The growth is made up entirely of young hyaline "Langhans" cells interspersed with syncytia. (Drawn from a slide of Dr. John Teacher's, with his kind permission.) Obj. 1 inch. Ocular No. 8. Camera Lucida.

### PLATE IV.

Section of chorionepithelioma of the uterus, associated with pregnancy. The growth is made up entirely of large mononuclear cells loaded with granules of glycogen and presenting a deeply chromatic nucleus. The cells are lying in masses amongst areas of blood clot and fibrin. (Drawn from a slide of Dr. John Teacher's, with his kind permission.) Obj. 1 inch. Ocular No. 8. Camera Lucida.

### PLATE V.

*The Author's Case*.—A portion of a metastasis in the liver. The tumour here consists of large syncytial masses and mononuclear cells of varying character. In the centre of the field is a pale area of laminated fibrin containing leucocytes. Elsewhere masses of blood are seen in which cell elements of the tumour are lying. The liver cells, seen below, are compressed and flattened. Obj. 1 inch. Ocular No. 8. Camera Lucida.

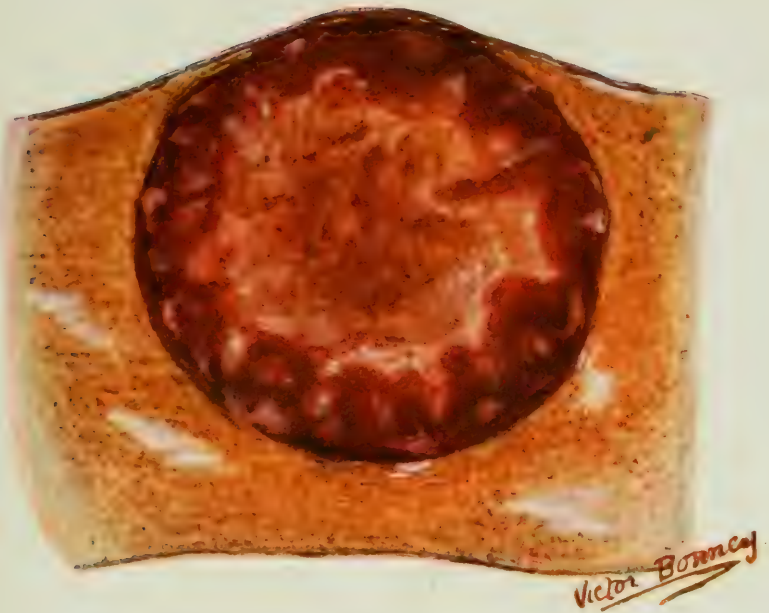
### PLATE VI.

*Schlagenhauser's Case*.—A portion of the testicular growth showing large "Langhans" cells, syncytial masses, and large mononuclear cells. (Drawn from a slide, with the kind permission of Professor Schlagenhauser.) Obj. 1 inch. Ocular No. 8. Camera Lucida.

### PLATE VII.

*Ritchie's Case*.—A portion of the tumour showing large "Langhans" cells and syncytia invading the substance of the teratoma. Above is seen a space lined by stratified epithelium. Masses of blood are scattered through the field. (Drawn from a slide, with the kind permission of Dr. Ritchie.) Obj. 1 inch. Ocular No. 8. Camera Lucida.

Plate I.



Hepatic Metastasis from Chorionepithelioma  
of Omentum.

*Victor Bonney*



Plate II.



Fig. 1.

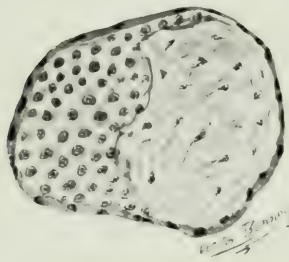


Fig. 2.

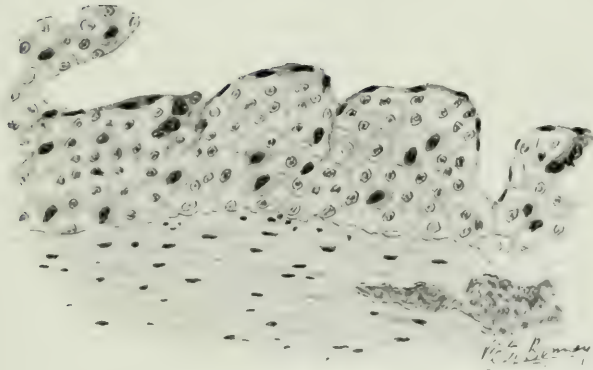


Fig. 3.





Plate III.





Plate IV.

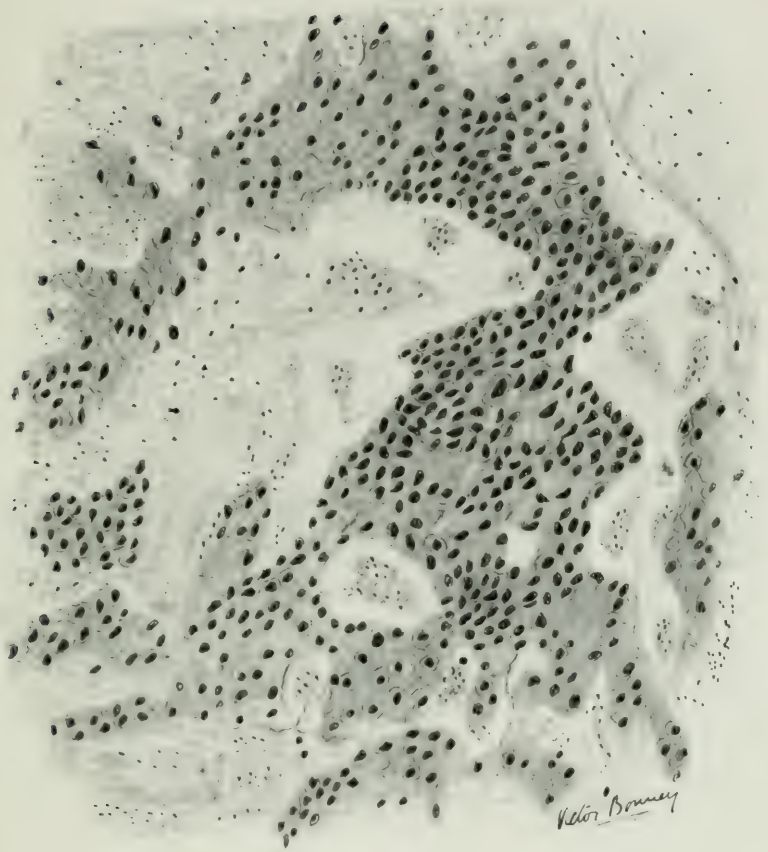






Plate V.

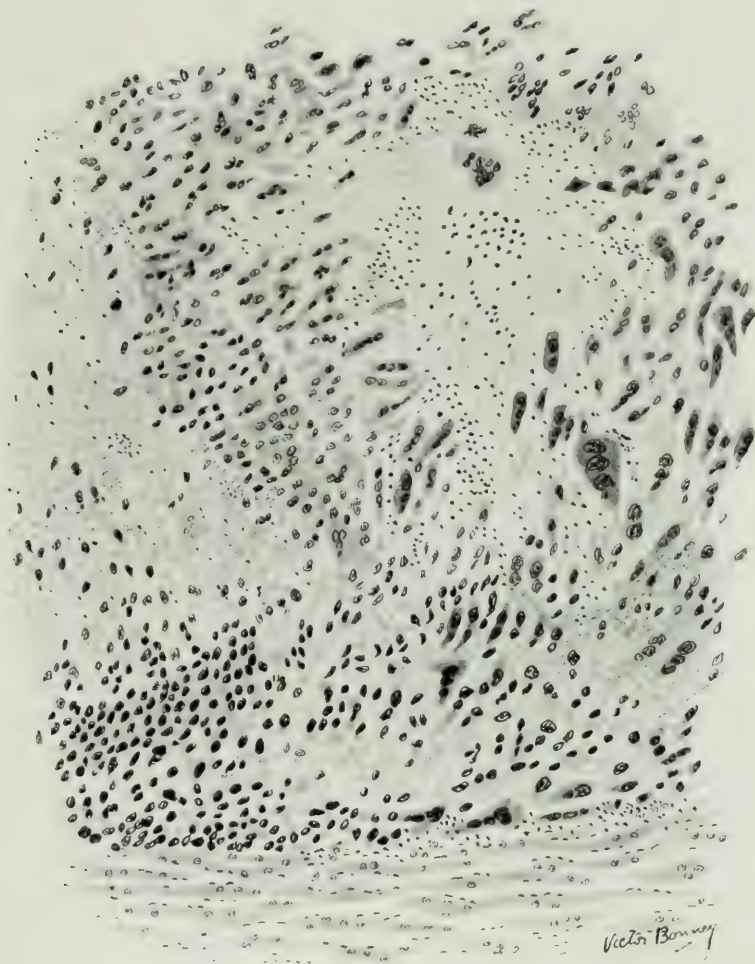




Plate VI.

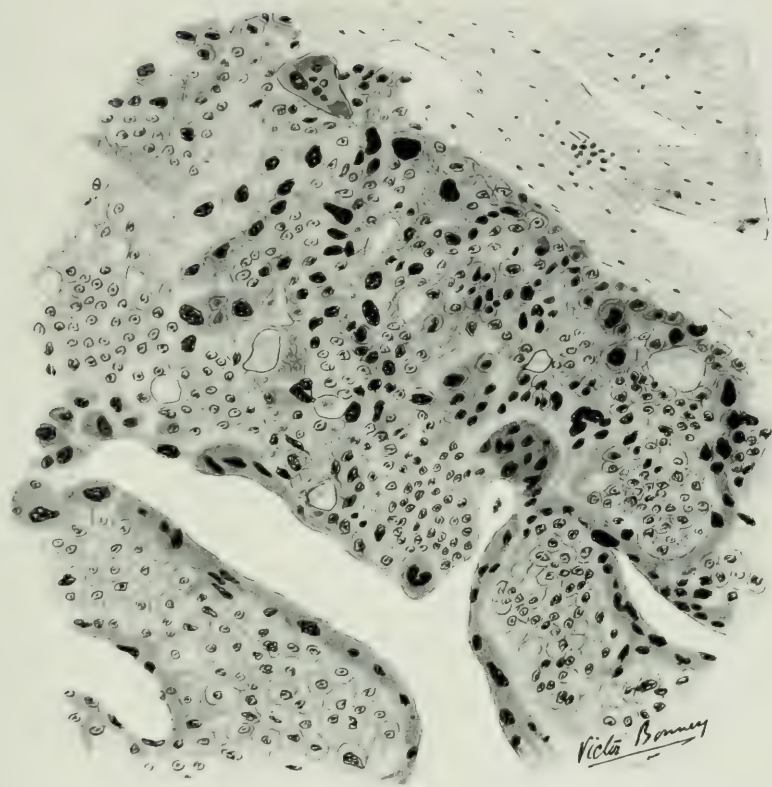






Plate VII.





# MENSTRUATION, CHILDBIRTH AND CANCER: A STATISTICAL STUDY BASED ON THE RECORDS OF THE MIDDLESEX HOSPITAL.

BY WALTER BALL, M.B., B.S.

## I.—GENERAL STATISTICS.

DURING the 10 years, 1895 to 1904, 1,492 cases of malignant disease in women are recorded in the clinical registers of the Middlesex Hospital. A history of the menstrual function was obtained in 984 cases, but in the remaining 508 cases no reference to the menstrual history was found.

The site of the primary growth in the 984 cases was as follows:—

Uterus	{Cervix 464}	.	.	.	.	.	.	504
	{Body 40}	.	.	.	.	.	.	
Vagina	.	.	.	.	.	.	.	9
Vulva	.	.	.	.	.	.	.	20
Ovary	.	.	.	.	.	.	.	30
Breast	.	.	.	.	.	.	.	285
Rectum	.	.	.	.	.	.	.	51
"Other Sites"	.	.	.	.	.	.	.	85

These classes of case will now be considered separately, and in some detail. The figures in brackets indicate the number of cases in which a statement concerning the factor in question is recorded. Deficiencies in the records account for the varying numbers. The entire series of statistics is tabulated at the end of the paper.

## II.—CANCER OF THE CERVIX UTERI.

(464 Cases.)

Of the 464 cases of cancer of the cervix which are recorded, 443 occurred in married women (398 parous, 45 nulliparous), and 21 in unmarried women.



These yield the following averages:—

Average number of pregnancies (parous women)	5·23
Mean age at birth of first child (287 cases)	22·29 years
"    "    "    last    "    (301    "    )	34·31    "
Average child-bearing period	12·02    "
Average number of miscarriages (204 cases)	1·9
Mean age at onset of catamenia (365    "    )	14·1 years
"    "    "    menopause (130    "    )	47·55    "
"    "    "    disease (396    "    )	45·25    "

Of the 266 cases constituting the difference between the numbers in which (a) the onset of the disease, and (b) the onset of the menopause, were noted, 22 were above the mean age of the menopause at the onset of the disease, and 244 were below. Consequently, the generally received opinion that cancer of the cervix occurs previously to the onset of the menopause is borne out by the records of the Middlesex Hospital.

**Menstrual History.**—In 428 cases menstruation was recorded as "regular"; of these, in 29 it was "scanty," in 56 "copious" or "excessive," and in 48 cases the flow is noted as being accompanied by pain.

In 30 cases menstruation was recorded as "irregular": of these in 2 cases it was "scanty," in 6 "copious," and in 6 cases the flow is recorded as being accompanied by pain.

In 3 cases menstruation was "irregular" before marriage, but regular afterwards, and in 3 cases it became irregular after marriage.

#### *Unmarried Women.*

(21 Cases.)

Mean age at onset of catamenia (18 cases)	13·91 years
"    "    "    menopause (6    "    )	45·83    "
"    "    "    disease (20    "    )	43·65    "

**Menstrual History.**—In 18 cases menstruation was recorded as "regular"; of these in 2 cases it was "copious," and in 3 the flow is noted as being accompanied by pain.

## III.—CANCER OF THE BODY OF THE UTERUS.

(36 Cases.)

Of the 36 cases of cancer of the body of the uterus which are recorded, 33 occurred in married women (24 parous, 9 nulliparous), and 3 in unmarried women.

Average number of pregnancies (parous women)	4.58
Mean age at birth of first child (18 cases)	25.2 years
„ „ „ last „ (16 „ )	35.06 „
Average child-bearing period	9.84 „
„ number of miscarriages (16 cases)	1.56
Mean age at onset of catamenia (27 „ )	14.5 years
„ „ „ menopause (20 „ )	48.15 „
„ „ „ disease (27 „ )	50.77 „

**Menstrual History.**—In 27 cases menstruation was recorded as “regular”; of these in 2 cases it was “scanty,” in 2 cases “copious,” and in 5 cases the flow is noted as being accompanied by pain.

In 5 cases menstruation was recorded as “irregular”; of these in two cases it was “scanty.”

In the 3 cases of cancer of the body of the uterus, which occurred in single women, menstruation was recorded as “regular.”

## IV.—SARCOMA OF THE UTERUS.

No case of sarcoma of the cervix is recorded.

Four cases of sarcoma of the body of the uterus are recorded, 3 in married women, and one in an unmarried woman. The married women were all parous.

In 3 cases the disease had its onset subsequent to the menopause; in the fourth case the onset was “1 year before the menopause.”

**Menstrual History.**—In 2 cases (married) menstruation is recorded as “regular”; of these in 1 case it was “copious.” In 1 case (married) it was “irregular,” and accompanied by pain, and in 1 case (unmarried) it was “regular.”

## V.—CANCER OF THE VAGINA.

Nine cases of cancer of the vagina are recorded, all were married, and of these 6 were parous.

In all the cases menstruation was recorded as "regular," and of these in 1 case it was excessive.

## VI.—CANCER OF THE VULVA.

(20 Cases.)

Of the 20 cases of cancer of the vulva which are recorded 19 occurred in married women (13 parous, 6 nulliparous), and 1 in an unmarried woman.

Average number of pregnancies (parous women)	7.15
Mean age at birth of first child (9 cases)	26.77 years
"    "    "    last " (8 " )	38.62 "
Average child-bearing period	11.85 "
"    number of miscarriages (10 cases)	1.5
Mean age at onset of catamenia (16 " )	15.31 years
"    "    "    " menopause (13 " )	48.07 "
"    "    "    " disease (16 " )	57.31 "

**Menstrual History.**—In 17 cases menstruation was recorded as "regular," and in 1 of these the flow is described as being accompanied by pain.

On comparing the parts of the generative tract already considered we note the following points:—

(a) The great frequency with which the disease attacks the cervix uteri (nearly 13 times as often as it attacks the body, and 23 times as often as it attacks the vulva).

(b) That it is particularly the cervix uteri of married women which is affected. Only 21 cases of the 464 recorded occurred in unmarried women, a number equal to 4.5 per cent. of the total, whereas the percentage of unmarried women over the age of 25 in the population of London at the last census was over 20 per cent. Hence, after making correction for the relative numbers of married and unmarried women in the population, it appears that a married woman is about five times as likely to suffer from cancer of the cervix as an unmarried woman.

(e) In cancer of the body of the uterus the average number of pregnancies is small (4·5) compared with the average in cancer of the cervix (5·2) and cancer of the vulva (7·1); moreover the average child-bearing period is only 9·8 years (cervix 12·02, vulva 11·85). These facts are remarkable, but at present one can only speculate as to their meaning.

## VII.—OVARY.

In all 29 cases of malignant growths affecting the ovary are recorded. Of these 9 were described as papilliferous cysts. The two varieties of growth will be considered separately.

### (A) CANCER.

Fifteen cases of cancer of the ovary were in married women, 5 in unmarried.

Average number of pregnancies (parous women 11 cases)	3·45
Mean age at birth of first child (5 cases)	21·8 yrs.
"    "    "    "    "    last    "    (4 cases)	33·4 "
Average child-bearing period	11·7 "
"    number of miscarriages (5 cases)	1·2
Mean age at onset of catamenia (15 cases)	14·67 "
"    "    "    "    "    menopause (9 cases)	48·0 "
"    "    "    "    "    disease (16 cases)	50·6 "

### (B) PAPILLIFEROUS CYST.

Nine cases of papilliferous cyst are recorded, all in married women.

Average number of pregnancies (parous women 6 cases)	1·5*
Mean age at birth of first child (3 cases)	22·3 yrs.
Average number of miscarriages (7 cases)	1·0
Mean age at onset of catamenia (9 cases)	15·9 "
"    "    "    "    "    menopause (4 cases)	48·5 "
"    "    "    "    "    disease (8 cases)	43·1 "

\* One of the cases bore 4 children, the remaining 5 bore each a single child. Hence the "mean age at birth of the *last* child is identical with that of the *first* child," and the "child-bearing period" of the preceding tables entirely disappears.

**Menstrual History.**—In 19 cases of cancer of the ovary menstruation was recorded as “regular;” of these in 4 it was “copious,” in 2 “scanty,” and in 3 cases the flow is noted as being attended by pain.

In 1 case of cancer of the ovary menstruation was irregular and profuse.

In the 9 cases of papilliferous cyst menstruation was regular.

In the one case of sarcoma of the ovary which is recorded, the woman was married but nulliparous. The disease appeared at the age of 61.

### VIII.—BREAST.

(285 Cases.)

Of the 285 cases of cancer of the breast recorded, 224 occurred in married women (172 parous, 22 nulliparous, 30 with no record on the point), and 61 in unmarried women.

Average number of pregnancies (parous women)	. 4.9
Mean age at birth of first child (172 cases)	. 25.25 yrs.
“ “ “ “ “ last “ (119 “ )	. 36.25 “
Average child-bearing period	. 11 “
“ number of miscarriages (109 cases)	. 1.4
Mean age at onset of the catamenia (173 cases)	. 15.23 yrs.
“ “ “ “ “ “ menopause (116 cases)	. 47.20 “
“ “ “ “ “ “ disease (260 cases)	. 48.94 “

**Menstrual History.**—In 249 cases menstruation was recorded as “regular;” of these in 17 it was “scanty,” 18 “copious,” and in 7 cases the flow is reported as being attended by pain.

In 20 cases menstruation was recorded as “irregular;” of these in 3 it was “copious,” and in 3 cases the flow is reported as being attended by pain.

### IX.—RECTUM.

(51 Cases.)

Of the 51 cases of cancer of the rectum which are recorded, 36 occurred in married women (35 parous, 1 nulliparous), and 16 in unmarried women.



Average number of pregnancies (parous women)	. 4.6	
Mean age at birth of first child (30 cases)	. 23.9	yrs.
.. .. . last .. (25 .. )	. 33.5	..
Average child-bearing period	. 9.6	..
.. number of miscarriages (19 cases)	. 1.26	
Mean age at onset of catamenia (34 cases)	. 15.11	yrs.
.. .. . menopause (28 cases)	. 45.92	..
.. .. . disease (29 married)	. 51.1	..
.. .. . (14 unmarried)	. 56.5	..

**Menstrual History.**—In 48 cases menstruation was recorded as “regular;” of these in 2 it was “scanty,” in 3 “copious,” and in 3 cases the flow is noted as being attended by pain.

In 3 cases menstruation was recorded as “irregular;” of these in 1 case it was “scanty.”

#### X.—“OTHER SITES.”

(55 Cases.)

Fifty-five cases of cancer are recorded in situations other than those already considered. Of these 45 occurred in married women (36 parous, 9 nulliparous), and 10 in unmarried women. The sites of the growth in these cases were as follows:—Stomach, 9 cases; face (rodent cancer), 7; maxilla, 5; tongue, 5; cheek, 4; colon, 3; cæcum, 3; liver, 2; bladder 2; larynx, 2; thyroid, 2; cervical glands, pharynx, tonsil, œsophagus, middle-ear, external auditory meatus, pancreas, gall-bladder, omentum, leg, one case each.

Average number of pregnancies (parous women)	. 7.5	
Mean age at birth of first child (26 cases)	. 23.3	yrs.
.. .. . last .. (25 .. )	. 38.4	..
Average child-bearing period	. 15.06	..
.. number of miscarriages (19 cases)	. 1.6	
.. age at onset of catamenia (39 cases)	. 14.9	yrs.
.. .. . menopause (25 married)	. 45.7	..
.. .. . (3 unmarried)	. 43.0	..
.. .. . disease (38 married)	. 54.34	..
.. .. . (8 unmarried)	. 38.12	..

**Menstrual History.**—In 47 cases menstruation was recorded as “regular;” of these in 1 case it was “scanty,” in 2



### **Menstruation with Reference to the Site of the Disease and the Mean Age of its Onset.**

A marked distinction shows itself between cancer of the generative tract and other situations. Thus the mean age of onset of the catamenia is earlier, and the mean age of onset of the menopause is later, in cases in which cancer affects the generative tract. Hence sexual life is longer in cases of cancer affecting the generative tract, and the difference amounts to as much as 2.9 years. Further, the mean age of onset of cancer affecting the generative tract is 48.4 years, while the mean age of onset of cancer affecting other parts is 49.56.

Making comparison between the cervix, the breast, and the rectum as being the commonest situations of cancer in women these differences become more marked. For the duration of sexual life is longest in cervix cases and the disease appears earliest, while in rectal cases the duration of sexual life is shortest and the disease appears latest. The corresponding facts with regard to the breast are intermediate between the other two.

### **Childbirth, with Reference to the Site of the Disease and the Mean Age of its Onset.**

Contrasting, as in the previous section, cancer of the generative system with cancer of other regions it appears that the mean age at birth of the first child is greater, the mean age at birth of the last child is less, in cases of cancer of the generative region than in cancer of other regions; consequently the average child-bearing period is less. Corresponding with these facts it is found that the average number of pregnancies is also less in cases of cancer affecting parts of the generative tract (4.3 as against 5.67). The average number of miscarriages is the same in both groups of cases.

Taking the cervix, the breast and the rectum as the commonest sites of cancer in females these points do not show themselves with corresponding exactness. Thus in cervix cases the mean age at birth of the first child is less than in cases of cancer of the breast or rectum, while the mean age of birth of the last child is intermediate, and the average

child-bearing period is greater. So also the average number of pregnancies and the average number of miscarriages in cases of cancer of the cervix are greater than the corresponding factors in cases of cancer of the breast and cancer of the rectum. The reason of these differences from the averages obtained for generative and non-generative groups of cases apparently lies in the extremely small average number of pregnancies and miscarriages in ovarian cases, and the large number that obtains in cases of the non-generative group other than the breast and rectum.

**Menstruation in Married and Unmarried Women Respectively with Reference to the Site of the Disease and the Mean Age of its Onset.**

Figures have been obtained for married and unmarried women in the case of cancer at the following situations:—cervix, breast, rectum, and “other sites.”

In the case of cancer of the cervix the mean age at onset of catamenia, of menopause, and of the disease, are earlier in unmarried than in married women; moreover, the mean duration of sexual life is shorter in the unmarried by 1.5 years.

In the case of the breast and of the rectum the same statements hold good, excepting that the mean age at onset of the disease in unmarried rectal cases is greater than in married rectal cases.

With regard to these factors in connection with cancer at “other sites” the number of cases in unmarried women is too small to speak with certainty, and moreover, probably contains some cases of sarcoma occurring in young subjects. The figures obtained, however, show that the mean age at onset of catamenia and of menopause is greater in unmarried women, while the mean age at onset of the disease is considerably less.

With regard to the character of the menstrual function itself in persons who ultimately become affected by cancer, the investigation has not shown any noteworthy peculiarities.

NOTE.—Most of the material on which the above paper is based was collected by Mr. J. Glenton Myler, formerly Registrar of the Cancer Department.



COLLECTIVE TABLE OF THE AVERAGES OBTAINED IN AN INVESTIGATION ON THE RELATION BETWEEN MENSTRUATION AND CHILD-BIRTH, AND CANCER.

SITE OF DISEASE.	Mean Age at Onset of		Mean No. of Pregnancies.	Mean No. of Miscarriages.	Mean Child-bearing Period in Years.	Mean Age at Birth of First Child.	Mean Age at Birth of Last Child.
	Catamenia.	Menopause.					
Cervix uteri { married ... unmarried ...	14.1	47.5	45.25	5.2	1.9	22.3	34.3
Body of uterus (all cases) ...	13.9	45.8	43.65	—	—	—	—
Vulva (all cases) ...	14.5	48.15	50.77	4.5	1.5	25.2	35.0
Ovary { (a) Cancer (all cases) (b) Papilliferous cyst (all cases).	15.3	48.0	57.0	7.15	1.5	26.7	38.6
Means of all Cancer of Generative System ...	14.67	48.0	50.6	3.45	1.2	21.8	33.5
Breast { married ... unmarried...	15.9	48.5	43.1	1.5	1.0	22.3	—
Rectum { married ... unmarried...	14.4	47.66	48.4	4.3	1.4	23.66	35.35
"Other sites" { married ... unmarried...	15.2	47.2	48.93	4.9	1.4	25.25	36.25
Means of all Cancer at Non-Generative Sites ...	14.7	47.1	48.4	—	—	—	—
	15.3	45.92	51.0	4.6	1.2	23.9	33.5
	14.4	45.62	56.0	—	—	—	—
	14.8	45.7	54.3	7.5	1.6	23.3	38.4
	15.6	46.0	40.9	—	—	—	—
	15.08	45.45	49.87	5.67	1.4	23.15	36.05



# MALIGNANT DISEASE OF THE LIP: A STATISTICAL STUDY BASED ON THE RECORDS OF THE MIDDLESEX HOSPITAL.

By C. W. ROWNTREE, M.B., B.S., F.R.C.S.

## I.—INTRODUCTION AND GENERAL STATISTICS.

SINCE 1853 there have been in the wards of the Middlesex Hospital 241 cases of malignant disease of the lip. This number is a comparatively small one, because (1) the number of males treated in the hospital for cancer of all kinds since this time (1853) is less than half the number of females, (2) the operation in vogue for cancer of the lip is of so simple a nature that only a small proportion of the actual cases are treated in hospitals—at all events when the lip itself is the sole visible seat of growth, and (3) because it is certain that in the past many of the cases have been dealt with as out-patients and of these there are now no systematic records.

Great care has been taken to avoid counting any case more than once, in view of the fact that re-admissions have been frequent.

Considering all the cases, we find that the proportion of cancer of the lip (241) to malignant growths occurring in all organs of the body (8,859) is 2·72%. In this percentage males (233 cases) account for 2·6% and females (8 cases) for ·1%.

Dealing with males alone malignant disease of the lip constitutes 6·8% of all malignant disease in men (3,414); in other words, in males 1 case in every 15 of malignant disease occurs in the lip.

The corresponding figures in females are 1 in every 714 cases. The relative frequency in the two sexes is as 29:1; in spite of the fact that the number of female cases is so small (8), this figure agrees fairly with that given by Roger Williams (33-1).

On the other hand Heinmann quoted by v. Bergmann gives the proportion, from an analysis of 509 cases, as 13:1; while Fricke from 1,338 cases gets the proportion 11:1, which would

almost suggest that cancer of the lip may be more frequent among women in Germany than it is in England.

## II.—CANCER OF THE LIP IN MALES.

### A.—Ætiological Factors.

*Age.*—In view of the remarkable variations in the duration of the disease in different individuals it was thought advisable in considering the question of age to take, not the age on admission, but to obtain the age of the patient at the time when the disease was first noticed. This was possible in 202 cases, the average age of which was 56·4 years.\* The youngest patient noted was a man of 29 and the oldest a man of 81. This, however, by no means represents the extreme limits, as several cases, in which the diagnosis was confirmed by microscopical examination, have been reported in children as young as 13, † while Mr. Jalland of York removed a carcinoma from the lip of a man aged 103. ‡

Below is a table showing the percentage occurrence of cases in the various quinquennial age-periods. Comparing the figures with those given for other sites of cancer § it is seen that cancer of the lip tends to occur at a later date than cancer in other situations, although the quinquennial period of maximum liability falls comparatively early, viz. 55–59.

—	25	30	35	40	45	50	54	60	65	70	75	80	85
	to	to	to	to	to	to	to	to	to	to	to	to	to
	29.	34.	39.	44.	49.	54.	59.	64.	69.	74.	79.	84.	89.

Lip.	No. of Cases. (202)	2	1	15	22	23	27	32	27	22	18	9	4	—
	Percentage ...	·9	·5	7·5	10·9	11·4	13·4	15·9	13·4	10·9	8·9	4·5	1·5	—

\* This is necessarily a lower figure than that given by Dr. Lazarus-Barlow in "Cancer Ages," *Arch. Middlesex Hosp.*, vol. v., p. 30, where the age on admission is alone dealt with, and is higher than that (52·4) given by Roger Williams, derived from a much smaller number of cases (100), *Med. Press and Circular*, 1889; but agrees closely with *Fricke* (Beiträge zur Statistik des Lippenkrebses, *Deutsche Zeitsch. f. Chir.*, Band 50), who from an analysis of 897 cases gives the age-period of maximum liability as 56–60. The age of the patients when first operated upon was taken in his series.

† Johnstone, *B.M.J.*, 1898, ii., and Batashoff, *B.M.J.*, 1898, ii.

‡ *B.M.J.*, 1891, i.

§ "Cancer Ages," *Arch. Middlesex Hosp.*, vol. v., p. 26.

|| *Fricke* (*Deutsche Zeitsch. f. Chir.*, Band 50) gives the quinquennium 56–60. The age of the patients when first operated upon was taken in his series.

*Occupation.*—As this disease has been called “countrymen’s cancer,” it was thought desirable to ascertain the usual dwelling-place of the patients; but as it was found that the only address given in the notes in the majority of cases was a London address where the patient was staying while waiting for admission into the hospital, the only guide we have is the occupation of the patients. This was given in 183 cases; 24 (13%) of these were agricultural labourers, whilst of the rest, 107 were general labourers, who, as nothing was stated to the contrary, were probably working in towns, and the remaining 54 had essentially town as distinct from country occupations.

This proportion of countrymen cannot be regarded as excessive when one remembers that at all events in the past, before the multiplication of provincial hospitals, the London hospitals drained a very large part of the surrounding country districts.

As regards the causation of the disease it cannot be said that an analysis of the occupations of the patients throws any light on the subject, but it is interesting to note that 2 of the 183 cases earned their living by playing wind instruments.

*Chronic Irritation.*—In many of the patients there had been sources of chronic irritation to which the onset of the disease was ascribed—

*Smoking and Chewing Tobacco.*—In 60 cases there was a note as to smoking; 51 were more or less heavy smokers, while on the other hand in the case of 9 patients it is definitely stated that they had never smoked. In the great majority of cases where the character of the pipe is mentioned it was of the unglazed clay variety.

In 6 of the smokers it was stated that the disease was situated on the opposite side to that on which the pipe was habitually held.

*Other Sources.*—In 11 cases, cuts by barbers, kicks, and other injuries were regarded as the cause of the trouble, and as immediately preceding the onset of growth. In 6 cases either a jagged tooth or an ill-fitting denture was in contact with the part of lip affected, while 3 cases gave a history of long-standing cracks of the lip.

**The Pre-cancerous State.**—In the following paragraph cases are included in which some pathological condition of the lip

obtained, which, from its apparent lack of change up to a certain date which was given by the patient with precision, may be regarded as non-malignant; and it is to be clearly understood that no case has been included in this list, however long the history or slow the growth, unless the patient gave a definite account of a pronounced change in character of the labial condition occurring at or about some definite period; this change usually consisting in a rapid increase in growth with ulceration.

This "pre-cancerous condition" was described in 4 cases as a "sore place" that had been present from 1 to 3 years, in 3 as a "pimple" that had been present from 1 to 6 years, in 6 a "wart" had been present several years, in 2 there had been a cracked lip from 1 to 4 years, in 1 case a cut by a barber had never healed, in another a dry peeling condition had been present 4 years, while in 4 cases ichthyosis had preceded the onset of ulceration. The association of ichthyosis and cancer of the lip is significant in view of its rarity, for in the throat clinique of the Johns Hopkins Hospital it was only seen twice in three years; while Schwimmer\* in an examination of 20,000 patients only saw what he calls Leucokeratosis Bucalis 20 times; of these 20 cases 4 are known to have subsequently developed cancer.

**Heredity.**—Notes as to heredity are for the most part lacking, but in one case homologous heredity is noted, the patient's brother having had carcinoma of the lip.

### B.—Clinical History.

From a consideration of 122 cases in which the date of onset was noted it was found that the duration of the disease previous to surgical treatment averaged 21 months, the shortest history being one of 6 weeks and the longest 15 years.

Subjoined is a table showing the cases classified according to the length of the history; it will be noticed that 42% of the cases presented themselves before the expiration of 6 months.

Under 3 Months.	4—6 Months.	7—9 Months.	10—12 Months.	1—2 Years.	2—3 Years.	3—4 Years.	4—5 Years.	5—6 Years.	6—7 Years.	15 Years.
18	34	8	17	20	8	5	5	2	4	1

\* Vrtljschr. f. Dermat. u. Syph., Wein, 1878.



This long delay in seeking relief for a condition obvious to the most casual observer can only be explained by the absence of pain or other symptoms until quite the later stages of this disease.

**Glandular Infection.**—A study of the condition on admission of 143 cases who had never undergone operation showed that 46% had obvious enlargement of the submental or submandibular lymph glands.

In 10 of these cases the date at which glandular enlargement first showed itself was stated, and the average was found to be 6·7 months after the appearance of the primary growth, the minimum period being 3 months and the maximum 2 years.

**Total Duration of the Disease.**—Certain of the cases (12) died in the hospital, never having undergone operation, and the average total duration of these from first to last was 24·5 months; the most acute case lasting only 8 months, while one man died 6½ years after first noticing the disease.\*

Below is an analysis of these 12 cases.

Under 1 Year.	Under 2 Years.	From 2—3 Years.	3—4 Years.	4—5 Years.	6—7 Years.
3 cases.	4 cases.	2 cases.	1 case.	1 case.	1 case.

In 20 cases who had been operated upon, yet died of the disease, the average total duration of life was 43·5 months, a difference between the unoperated and operated cases of 20 months.

In 16 of these 20 cases the operation was confined to the lip, while in 4 cases the glands were removed at the same time; in one case, the total duration of which was only 13 months, the glands were noticeably enlarged at the time of operation on the lip, but were not removed.

### C.—Pathological Anatomy.

**Site of Growth.**—In reference to the relative frequency with which the two lips are attacked, 211 cases present satisfactory information on this point. Amongst these 205 showed

\* The case mentioned above as lasting 15 years, was operated upon, and nothing more was heard of him; one naturally has some doubt as to whether the condition was malignant for the whole of that period.



disease of the lower lip, while in 6 the upper lip was the seat of disease; hence, according to the records of the Middlesex Hospital the lower lip is the seat of cancer 34 times as frequently as the upper. This figure agrees closely with that (30:1) given by Roger Williams and Fricke (31:1).

In 179 cases further particulars were given, and in 6 cases where the upper lip was affected the growth was in 4 cases to the right of the middle line and in 2 cases to the left. In none of the cases where the upper lip was affected was the growth at or about the middle line. In the lower lip 75 cases were to the right of the middle line and 72 were to the left, while in 26 cases the growth was stated to be at the centre of the lip.

In 4 of the cases the growth was at the angle of the mouth, 2 at the right and 2 at the left; there is some doubt, however, as to whether these cases really started at the angle or at the extreme end of the lower lip.

It will be seen from the above figures that the two sides of the lips have an equal tendency to be the seat of cancer, and that 80% of the cases occur in that part of the lip between the centre and the angle of the mouth. This point has already been drawn attention to by v. Bergmann.

In 49 of the total cases, the site of origin of the growth was described with exactness according as it arose from the muco-cutaneous surface of the lip, from the red line of junction of skin and mucous membrane, or from the buccal surface. The numbers for sites are as follows:—From the muco-cutaneous surface 34 cases, from the red line 12 cases, and from the buccal surface 3 cases. Thus cancer affects the muco-cutaneous surface in 68% of all cases.

No case of growths symmetrically placed on the upper and lower lip has occurred at the Middlesex Hospital.

**The Cause of Death in Cancer of the Lip.**—There are records of 34 autopsies on these cases, and the cause of death was found to be in 29 cases some pulmonary condition, such as Œdema, Broncho-pneumonia or Gangrene, in 2 cases Œdema of the glottis, in 1 case Hæmorrhage, and in 2 cases an intercurrent affection.

Two of the examinations were on women, 32 on men, and in 9 cases it was found that secondary deposits other than in

the submaxillary or cervical glands were present (all in males).

In all cases the glands in the anterior triangle of the neck were affected to a greater or less extent, and in 19 cases it is noted that the deep cervical glands were also the seat of growth.

In one of the cases which died with recurrence in the neck, the lip itself had remained free from growth.

Below is a table showing the distribution of the metastases in the 9 cases:—

Case.	C. <sup>1</sup>	A. <sup>1</sup>	B. <sup>1</sup>	M. <sup>1</sup>	Mes. <sup>1</sup>	Lungs.	Liver.	Kidney.
1	..*	..*						..*
2						..*		
3						..*		
4								..*
5	..*							Femur.*
6	..							Thyroid.
7	..					..	..	Larynx and Brain.
8	..			..	..	..	..	Adrenal Heart and Pancreas.
9	..	..					..	

In those cases marked with an asterisk no microscopical examination of the secondary deposits was carried out.

**Recurrence after Operation.**—Of the 233 male cases with which this paper is concerned there are full notes in 217 cases, and it was found that on admission 20 (9%) were inoperable, and had never undergone surgical treatment.

71 (33%) of the cases had been operated upon in other institutions, and of these 43 (20%) were inoperable upon admission here, while the other 28 (13%) were again submitted to operation.

The remaining 126 cases had undergone no previous treatment, and were operated upon here. Of these, 23, or 18%, came back at a later date with recurrence.

Looked at in another way, we find that of 146 cases who had never had surgical treatment and who presented them-

<sup>1</sup> C = Cervical glands; A = axillary; B = bronchial; M = mediastinal; Mes. = mesenteric.

selves at the Middlesex Hospital, 20 or 13·5%, were in too advanced a state to be operated upon; while, as mentioned above, the remaining 126 (86·5%) were operated upon, and of these 23 (18%) returned with recurrence. As to the rest, except in a few isolated instances, nothing is known, but if we may judge by the fact that so many as 71 cases came here after having been operated upon elsewhere, even taking into account the special cancer wards at this hospital, it seems highly probable that many cases, operated upon here for the first time, have recurred and gone to other institutions for further treatment.

Of the cases coming to the hospital with recurrence, who had been operated upon either here or elsewhere, it was possible in 77 to ascertain the nature of the operation which had performed.

It was found that in only 7 cases had the first operation included excision of the glands. In these cases the recurrent growth was in 1 case local, in 1 case in the submaxillary glands alone, and in the remaining 5, in both lip and glands.

Of the other 70 cases, in 30 the patient was free from local recurrence, secondary growth having taken place in the submaxillary glands; in 20 cases there was recurrence in both lip and glands, while in the remaining 20 recurrence was in the lip, the glands showing no signs of involvement. Of these last 20 cases, 3 had had more than one operation: in one case the second operation taking place five years after the first, recurrence occurring after a further interval of two years; in the second case the second operation was after an interval of three years, recurrence showing itself again in two years; while in the third case the growth recurred after three months, was removed, recurred again in six years, was again operated upon, and recurred for the third time.

**Date of Recurrence.**—As to the date after operation at which recurrence took place in the lip, the average period is 24 months, in the glands 17 months. In these figures are included a few cases in which the operation on the lip was admittedly imperfect, leading to return of growth in a very few weeks.

In one case recurrence in the lip took place after a lapse of 16 years, while in another case the submaxillary glands showed

signs of involvement 11 years after the primary growth had been removed, the lip remaining free from growth.

**Operation in Cancer of the Lip.**—There have been 126 operations on cases of primary cancer of the lip in the Middlesex Hospital.

The operative procedure carried out in the majority of instances consisted in removal of the growth by means of the simple **V** incision; in only 17 instances was ablation of the submaxillary glands attempted. If we may argue from the fact that out of 70 cases of recurrence, in none of which an operation on the glands had been performed, 30 cases were free from local recurrence, the conclusion must be drawn that a routine excision of the submaxillary gland-bearing area, even when there is no obvious enlargement of the glands, would result in a materially lessened tendency for recurrence to take place.

**Extension of Growth.**—A study of 60 cases of advanced cancer of the lip, 40 of which died in the hospital, and the other 20 cases being in such a condition when last seen as to show that death was not far distant, gave the following results:—

In 22 cases the lip was free from recurrence, growth being present only in the glands.

Of the other 38 cases, in 18 ulceration spreading in an inward direction had involved the mandible and floor of mouth, and in two instances the tongue.

In 4 cases growth had travelled round the angle of the mouth, so reaching the upper lip, while in 8 cases growth had extended directly outwards, destroying portions of the cheek.

In 8 cases the ulceration had spread in a downward direction, reaching the chin; and in 2 cases ulceration from the lip had become continuous with the ulceration due to the breaking down of the submaxillary glands.

The general tendency appears to be for a growth of the lower lip in the first place to extend outwards along the margin to the angle of the mouth of the corresponding side, subsequently to extend to the cheek, and finally to extend downwards towards the chin and submaxillary region. In the later stages the growth also extends inwards, fixes the



tissues of the lip to the jaw, and ultimately leads to involvement of the floor of the mouth.

In only 3 cases was there direct continuity of ulceration between the lip and submaxillary region, either through the floor of the mouth or over the external skin surface.

**Recurrence in Situ.**—As throwing some light on the method of extension of carcinoma of the lip we may consider the exact site of the second growth in those cases where local recurrence followed operation. We have precise particulars of 51 such cases.

In 29 cases the recurrence was said to be *in situ*, in 4 of these, however, there was growth on the inside of the lip only. In 14 cases the recurrent growth was not actually in or at the scar of the former operation, but to one or other side; in one case as much as half an inch away, in another a quarter of an inch, and in others 'a little distance,' 'just to one side,' etc. In one of these cases there was a small growth 'on each side of the scar'. In one case recurrence took place in the lower angle of the wound, while in another the recurrent growth was midway between the chin and the lower end of the scar. In another case recurrence took place in the gum opposite the scar in the lip, while in 3 cases growth recurred in the cheek by the angle of the mouth. In two further cases there was said to be a recurrent growth in the body of the mandible, apparently some little distance from the primary growth.

This tendency for the growth to recur at a point a little distance from the original site of disease—a phenomenon well known in the breast for instance, but about which most modern writers are silent—was drawn attention to by Erichsen in 1840, in the following words: 'Of the very many patients that have been operated upon at the University College Hospital, I have known but few return with recurrence. When return does take place, it is not always in the cicatrix or in the adjacent glands. I have seen it at the angle of the mouth and inside the cheek of the side opposite that from which the primary disease had been removed, and the recurrence not till three or four years after the operation'—a statement except in so far as it applies to the frequency of recurrence after operation, abundantly borne out by the records of the Middlesex Hospital cases.



A few of the cases are of sufficient interest to justify a detailed account.

J. S.—Had an ulcer on the right side of lip for seven years; this was excised, and one year afterwards another growth appeared on the opposite side, which was excised after an interval of nine years, the submaxillary glands having become involved.

W. B.—Admitted with an ulcer on the right side of lower lip, which had been present  $3\frac{1}{2}$  years. This was excised, and in  $4\frac{1}{2}$  years a small warty growth appeared on the opposite side.

J. W.—Excision of a warty growth, which had been present 2 years, from the left lower angle. Three months afterwards an ulcer appeared on the right side, and within a year the original growth recurred *in situ*, both tumours were then removed, recurrence taking place in the glands in 6 months.

J. L.—Warty growth on the right lower lip the size of a filbert nut, and on the left side a similar growth the size of a pea. Submaxillary glands involved.

W. B.—Two distinct warty growths on the lower lip, one on each side of the middle line and separated by apparently healthy mucous membrane. The growth on the left side had been present 12 months, and that on the right 8 months. The lip was excised, and he returned in two years with a growth just inside the right angle of the mouth. This was removed, along with the submaxillary glands, and in four years he again returned with recurrence on the inner surface of the upper lip on the right side. A third operation was undertaken, and five years afterwards he once more presented himself, this time with an inoperable growth of the tongue.

R. L.—An ulcer the size of a shilling on each side of the lower lip near the angles of the mouth. That on the right side of 2 months' duration, and that on the left 3 months. The right submaxillary glands were enlarged and removed with the lip, recurrence taking place on the right side locally, and in the glands.

The light in which the pathology of these cases must be regarded is uncertain. In the first three the second growth may be regarded as independent of the primary growth; or they may be included among the cases of recurrence where

the recurrent growth is more distant from the primary site than is usually the case. A consideration of what has been said above as to the site of recurrence certainly suggests the latter view of the case.

As to the three cases in which two separate growths were present when the patient first came for treatment, it will be noticed that in none of the cases did the growths appear simultaneously, but that in each case one preceded the other by a few months; and it will further be noticed that in two of the cases growth first showed itself on the left side of the lip, that the second growth appeared on the right side, and that after excision recurrence took place, not at the site of primary growth, but at the right angle of the mouth and in the right submaxillary glands.

It is possible that these cases indicate, not the existence of double primary or pluricentric growths, but that extension of growth, instead of taking place along the surface of the lip, had done so by travelling along the subcutaneous tissues, possibly in the manner in which Mr. Handley suggests that it takes place in the breast.

### CANCER OF THE LIP IN FEMALES.

The number of cases is small, only 8 having been inmates of the hospital.

*Age.*—The average age of these cases was 50 years, the age-period of maximum liability being 50 to 54. Compared with the male cases it will be seen that the figures for women are lower by 6 years as regards the average age while the age period of maximum liability is lower by a quinquennium. The youngest patient was 35 and the oldest 66.

*Pathology.*—The upper lip was affected in 2 of the 8 cases, a proportion of 25%,\* which is much greater than the corresponding proportion in men (3%).

*Ætiology.*—In 1 only of the 8 cases is it stated definitely that the patient was in the habit of smoking. No other fact bearing upon the ætiology of the disease in women is recorded. The only other point that need be mentioned is that in one case a wart had been present on the lip for

\* This figure agrees closely with that given (32%) by Fricke, who collected 119 cases of cancer of the lip in women (*loc. cit.*).

20 years, which suddenly began to grow more rapidly 6 months before admission.

### THE HISTOLOGY OF MALIGNANT DISEASE OF THE LIP.

Microscopic examination of tumours removed from the lip has been carried out in 51 cases, and the slides are available for collective investigation.

In 2 of the cases the growth was rodent cancer, in the other 49 it was of the squamous-cell variety.

Of these 49, 31 may be said to present the typical picture of squamous-cell carcinoma, possessing three distinct types of cell—the Malpighian, the prickle, and the keratinizing—in varying proportions, and showing in each case either well-marked cell nests or a tendency to their formation.

In 2 of the cases the only type of cell present was the Malpighian, while in 4 cases the growth consisted entirely of prickle cells. These are the only examples in which the growth consisted solely of one type of cell; in 3 cases the Malpighian layer appeared to be absent, while in 3 others it was very insignificant. One case showed a transition from the Malpighian layer to keratinization without the interposition of a definite prickle layer.

As regards the nature of the growth in the glands, in the majority of cases where they had been removed by operation nothing was seen on microscopic examination but evidences of chronic irritation; in those cases, however, in which growth was present, its microscopical characters were the same as those of the primary growth, except that in a few instances cell-nest formation was better marked in the glands than it had been in the primary growth.

In certain of the cases both the primary growth and the recurrences were available for examination, and in these the same rule held good as with the glands, viz. that the recurrent growth was in all respects the same as the primary as regards the number and type of the cellular layers present.

# MALIGNANT DISEASE OF THE TONGUE: A STATISTICAL STUDY BASED ON THE RECORDS OF THE MIDDLESEX HOSPITAL.

By C. W. ROWNTREE, M.B., B.S., F.R.C.S.

## I.—INTRODUCTION AND GENERAL STATISTICS.

THE present communication is based on a study of 502 cases of primary malignant disease of the tongue, which have been in the wards of the Middlesex Hospital during the period 1855–1904 inclusive. Previous to that date the notes are so incomplete as to render it impossible to decide whether a growth described as cancer of the tongue arose primarily in that organ or in the neighbouring parts, a distinction which has, as far as possible, been rigidly made in the cases now under discussion.

Taking all cases (male and female) since 1855 we find that the proportion of primary malignant diseases of the tongue (502 cases) to malignant growths of all organs of the body (8,739 cases) is 5·7 per cent. Of this percentage malignant disease of the tongue in males (436 cases) accounts for 5·0 per cent., and in females 7 per cent. (66 cases). During the same period the number of in-patients admitted to the hospital was 126,309, giving the proportion of patients suffering from malignant disease of the tongue to in-patients admitted for all causes as 4 per cent.

Dealing with males alone, cancer of the tongue constitutes 12·6 per cent. of all malignant disease (3,380 cases); in other words, in males, of 8 cases of cancer 1 affects the tongue. In females, the corresponding figures are 1·2 per cent. malignant disease of the tongue to malignant disease of all organs (5,359); hence, in females cancer of the tongue constitutes about 1 case in every 83 of malignant disease.

Taking the entire series of cases from 1855 the relative frequency in the two sexes is, according to the Middlesex Hospital records, as 6·6 to 1.

## II.—ÆTIOLOGY.

**Age.**—In dealing with the question of age, with a view to greater accuracy only those cases have been considered in



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which a record obtains of the duration of the disease before admission.

In men this was so in 339 cases, and in these the mean age at onset was found to be 53·9 years, the youngest patient being 26, and the oldest 85. In the case of women, particulars were given in 50 cases, the mean age being 50·2, the youngest patient 28 and the oldest 75.

Below is given a table showing the cases arranged in quinquennial age-periods.

Age-Period.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.	80 to 84.	85 to 89.
Males—													
Cases ...	1	3	11	39	63	76	55	48	27	11	4	—	1
Per cent. ...	·3	·9	3·2	11·5	18·3	22·7	16·2	14·1	8·0	3·2	1·2	—	·3
Females—													
Cases ...	2	3	5	5	8	11	4	5	5	1	1	—	—
Per cent. ...	4·0	6·0	10·0	10·0	16·0	22·0	8·0	10·0	10·0	2·0	2·0	—	—

It will be noticed that both in the case of men and women the greatest number of cases occurs in the quinquennium 50-54, and that the mean age in both sexes (males 53·9, females 50·2) falls within this age-period of maximum liability.

**Heredity.**—In the case of women the presence of a cancerous family history is noted in 11 cases. There was one example of homologous heredity, the patient's mother having died of cancer of the tongue. In another case there was a history of cancer on both sides of the family; this patient was affected at the age of 36. The average age at onset of the disease among the female cases in which there was a family history of cancer is 41·7 years, which is 10·6 years earlier than among female cases where there was no such history (52·3 years).

In men a family history of malignant disease was obtained in 23 cases, in 7 of which homologous heredity was noted (cancer of tongue, once in grandfather, once in father, once in mother, twice in brother, once in cousin, and once in uncle). In one case the patient stated that 5 other members of the immediate family had died of cancer in various sites. The average age of the cases in which a history of cancer was



obtained is 51·3 years, which is less by 2·8 years than in the remaining cases (54·1 years).

**Occupation.**—An investigation of the occupation of the female cases gives no information, the great majority being engaged merely in house-work. In the case of the men, out of 289 cases in which the occupation is given, 24·5 per cent. were of the “unskilled labour” class, 58·8 per cent. were constituted by skilled mechanics, indoor servants, coachmen, and shopkeepers; the occupations of the remaining 16·7 per cent. were chiefly of a clerical nature.

**Smoking and Chewing Tobacco.**—In men the presence or absence of the habit of smoking was noted in 150 cases, in only 5 of these was it stated that they had never smoked. In most of the cases in which the variety of pipe is mentioned, it was a common “clay,” in two of these cases it was pointed out that the disease originated on the side opposite to that upon which the pipe was habitually held.

In no case in women was it stated that the patient had been in the habit of smoking or chewing tobacco. In 6 it was definitely stated that they had never smoked.

**Other Ætiological Factors.—Chronic Irritation.**—In 67 cases various sources of chronic irritation were adduced as possible causes of the malignant growth. These were in 53 cases the presence of a rough or decayed tooth in contact with the part affected, in 4 a rough tooth-plate was opposite the growth, in 8 the tongue had been bitten at the part which subsequently gave rise to the growth, in 1 the sore was attributed to the irritation of a pipe, and in another the patient stated that caustic placed in a decayed tooth had given rise to ulceration.

**Syphilis.**—In 77 of the 502 cases (15·3 per cent.) it was definitely noted that the patient had previously suffered from syphilis, while in 73 cases (14·5 per cent.) it was stated that the patient had not suffered from this disease. In the remaining 352 cases there was either no note or it was simply stated that the patient had suffered from “no previous illness.” Thus, of 141 male cases, in which satisfactory details were given, in 76 there was a history of previous syphilis, while the remaining 65 were said not to have suffered from this disease; and in women of 9 cases in which there was a definite statement, in only 1 was the history positive.

In 17 of the cases it was stated that at some period or other the tongue itself had been the seat of a syphilitic lesion excluding ichthyosis.

**Ichthyosis.**—In view of the importance which has been attached to the presence of ichthyosis linguæ as a factor in the ætiology of cancer of the tongue, the notes have been carefully examined with reference to this point. There were altogether 51 cases in which either its presence was indicated in so many words or in which the description of the condition present leaves no doubt that there was a lesion of the mucous membrane which would now receive the name of ichthyosis or one of its numerous synonyms.

Out of these 51 cases there were 18 in which there was a distinct history of syphilis, in 15 syphilis was definitely stated to have been absent, while in the remaining 18 there was no precise statement.

In connection with the latter group it is probable that certain observers holding views as to the essentially syphilitic nature of ichthyosis, would, on noting its presence, consider it unnecessary to specify that the patient had suffered from syphilis.

The relative numbers of the cases in which ichthyosis accompanied cancer of the tongue are in males (48 cases), 1 in every 9, and in females 1 in 22 (3 cases).

*The Position of the Malignant Growth in Ichthyotic Cases.*—Of the 51 ichthyotic cases the dorsum of the tongue was the seat of growth in 25. Hence, 50 per cent. of the ichthyotic cases show the growth on the dorsum. Since the dorsum is only affected in 9·6 per cent. of all cases of lingual cancer the close relationship between ichthyosis and cancer of the tongue is unmistakable.

**Pre-cancerous States.**—In addition to the cases of ichthyosis (51), and the cases (17) in which the tongue had been the seat of syphilitic lesions, 24 cases were recorded in which some pathological condition which, from its chronicity and lack of obvious change over a long period of time, may be justly regarded as non-malignant, preceded the onset of cancerous ulceration.

These were as follows:—In 7 cases there was a “pimple” or wart, which had existed unchanged for periods varying

from 15 months to 30 years; in 12 cases the tongue had been subject to ulcers or cracks for some time previously; in 3 cases a white patch had been present for 2 to 8 years, while in another case a persistent brown fur had been present 20 years. Lastly, in one case a growth, said to have been innocent, had been removed at another hospital  $2\frac{1}{2}$  years previously.

### III.—PATHOLOGICAL ANATOMY.

**Site of the Primary Growth.**—The total number of cases in which particulars as to the site of origin of the growth are given is 320 males and 48 females. Of these in 22 cases (all males) the growth arose on the under surface of the tip of the organ, in 17 cases (16 males and 1 female) in the middle line of dorsum; while of the remaining 329 cases, 159 (140 males and 19 females) arose to the right of, and 170 (142 males and 28 females) arose to the left of, the middle line.

Amongst those cases which originated on one or other side of the middle line (329 cases) the exact situations were as follows:—

Site of Growth.	Left of Middle Line. (Total, 142 Males, 28 Females.)		Right of Middle Line. (Total, 140 Males, 19 Females.)	
	Males.	Females.	Males.	Females.
<i>Dorsum—</i>				
Anterior third ... ..	0	0	1	1
Middle " ... ..	6	0	2	0
Posterior " ... ..	1	0	2	0
No further description ...	11	0	6	2
<i>Edge—</i>				
Anterior third ... ..	2	2	5	1
Middle " ... ..	14	7	20	4
Posterior " ... ..	4	1	5	0
No further description ...	17	2	21	2
<i>Under surface—</i>				
Anterior third ... ..	2	0	0	0
Middle " ... ..	2	0	2	1
Posterior " ... ..	2	1	0	0
No further description ...	5	0	9	0
<i>The side only mentioned—</i>				
Anterior third ... ..	9	3	6	0
Middle " ... ..	18	2	11	2
Posterior " ... ..	9	2	13	1
No further description ...	40	8	37	5

From the preceding table it appears (1) that the commonest site for cancer of the tongue in both sexes is the middle third of the edge, and (2) that both sides of the tongue are equally liable to be affected.

**Character of the Growth when first noticed.**—In 88 cases the patient was able to describe with some exactness the appearance of the growth when first noticed.

In 22 it was described as a small "ulcer" or "sore place"; in 44 as a small "wart" or "pimple," usually said to be "the size of a pea"; in 4 as a "crack," 8 as a "blister," 5 as a "white speck," 3 as a "black. tender spot," 1 as a "small raised red patch," while in 1 it was said to have started as a lump in the substance of the tongue. In 5 cases (included above) a definite history was given of the formation of a small tender blister which, after enlarging, bursting, and discharging a little "matter," left an ulcer that continued to increase in size and became indurated.

In one case there were said to be two small growths on the dorsum of the tongue, separated by about an inch of apparently healthy tissue. One growth had preceded the second by one month.

**Glandular Invasion.**—Of 327 patients who had never undergone operation, and concerning whom there is a note as to the condition of glands, it was found that in 264 cases there was enlargement of the cervical glands, and in 63 cases no glandular enlargement could be detected.

The mean period after the onset of the disease at which (according to the patient's statement) glandular enlargement first showed itself was found (46 cases) to be 7.6 months. The mean length of time that the disease had existed previous to admission in those cases which, on admission, showed no signs of affection of the glands, was 5 months.

#### **Post-mortem Examinations and Secondary Deposits.**

Post-mortem examinations have been made in 162 cases of cancer of the tongue dying in the hospital, of these 15 were in women. All the female cases showed metastasis in the cervical glands, and in this situation only.



*Table showing the distribution of Metastases in 147 Autopsies of Cancer of the Tongue (Males).*

Cervical glands . . . . .	145
Supraclavicular glands . . . . .	2
Axillary glands . . . . .	1
Retropharyngeal glands . . . . .	1
Bronchial glands . . . . .	1
Mediastinal glands . . . . .	1
Larynx . . . . .	4
Thyroid gland . . . . .	1
Lungs . . . . .	7
Pleura . . . . .	4
Heart . . . . .	2
Pericardium . . . . .	1
Liver . . . . .	8
Spleen . . . . .	1
Kidneys . . . . .	4
Suprarenals . . . . .	3
Diaphragm . . . . .	1
Occiput . . . . .	1

It is impossible to give exact figures as to which particular set of cervical glands was affected; the note on this point being in the majority of cases "submaxillary and cervical glands involved."

#### IV.—CLINICAL OBSERVATIONS.

**Duration of the Disease before Admission to Hospital.**—The average period after the disease was first noticed at which the patients came to the hospital for treatment was found in 378 cases (male and female) to be 8·3 months. Below is a table which shows that the large majority of the cases present themselves for treatment before the expiration of 6 months.

*Table showing the date after "onset" of the Disease at which Patients applied at Hospital for Relief (378 Cases).*

Months after the onset	0—3	4—6	7—9	10—12	13—18	19—24	over 24
No. of cases . . . . .	117	113	41	55	26	15	11



**Early Symptoms.**—While in the majority of cases the patient's attention was first attracted to the tongue by pain or tenderness, in no less than 8 cases was enlargement of the cervical glands the first objective symptom; and in 2 cases, one of which was under skilled observation for a prolonged period, constant local pain in the tongue definitely preceded all macroscopic change. Difficulty in swallowing was the patient's first complaint in one case, and in another, sudden great swelling of the tongue drew attention to the fact that it was the seat of a cancerous growth.

**Total Duration of the Disease.**—90 patients died in the wards of this hospital from cancer of the tongue, none of whom had had operative treatment; the average duration of life in these cases from the first onset of the disease until death was 14·5 months. In 37 cases who had been operated upon and subsequently died with recurrence, the total duration of the disease, from first to last, was 17·1 months. Operation therefore appears to prolong life by 2·6 months.

**The Cause of Death.**—189 patients have died in the wards of the hospital from cancer of the tongue; of these 19 were women. The actual cause of death may be classified as follows :—

	Males.	Females.
Pneumonia and Broncho-pneumonia	73	7
Gangrene of lung . . . . .	8	3
Œdema and Congestion of lungs . .	18	2
Bronchiectasis . . . . .	1	1
Empyema . . . . .	1	0
Œdema of larynx . . . . .	5	0
Hæmorrhage . . . . .	9	0
Chloroform Syncope . . . . .	2	0
Post-operative Sepsis . . . . .	5	0
Tuberculosis of lung . . . . .	4	0
Granular kidney . . . . .	2	1
Emphysema . . . . .	3	1

In 43 cases no special cause of death was stated, while in 3 of the above cases the presence of co-existing conditions, such as anterior mediastinitis, pericarditis, and pleurisy, all of which may be justly attributed to the extension of inflammatory processes from the mouth and cervical regions, was noted.

### Operations.

The operations which have been carried out in cases of cancer of the tongue may, in the first place, be considered according as they were undertaken with a view to the extirpation of the disease or merely as palliative measures for the relief of symptoms.

Of the latter class of operation, which was only performed in the period 1850-70, the only example mentioned is division of one or both lingual nerves, which was carried out in 9 cases; in 3 of these there was considerable alleviation of the pain and salivation,—the two most distressing symptoms,—in 3 there was slight improvement for a little while, in 1 the operation was quite ineffective, while in the remaining 2 death resulted as an immediate consequence of the proceeding.

The radical operations that have been performed allow of a certain amount of classification in spite of the fact that each surgeon varies his procedure to meet the exigencies of the particular case, and that no set operative procedure is applicable to every case of tongue cancer.

The cases have been classified on the following lines:—

(i) Cases in which the operator removed the obvious *disease* usually by a 'wedge' incision. Of this operation there are 15 examples, and of these 1 died from asphyxia due to the hæmorrhage during the operation.

(ii) Cases in which half or the whole tongue was removed through the mouth; these may be further subdivided according as this was effected by dissection (Whitehead's operation), or by means of one or other of the *écraseurs* which have been in use from time to time.

(iii) Cases in which not only the tongue and the submaxillary glands were removed, but in which an attempt was made to remove all the lymphatic-bearing tissues between these parts: this was usually done by means of Kocher's method, or a modification: in some cases the whole tongue, in others, half, with the floor of the mouth and submaxillary glandular area of the affected side, were removed.

Below are given all cases which were surgically treated; these are classified according to the type of operation

undertaken, and the mortality for each type of operation is given :—

—	Cases.	Deaths.	Per cent
Excision of "Wedge" ... ..	15	1	6·6
Whitehead's operation, with or without excision of glands ... ..	88	6	6·8
Whitehead's operation, with preliminary laryngotomy or tracheotomy... ..	21	3	14·2
Écraseur ... ..	35	5	14·2
Kocher's operation ... ..	32	9	28·1

[The above table of mortality includes all cases in which death occurred within 14 days after the operation.]

**Recurrence after Operation.**—In 427 of the cases admitted to the hospital full particulars of the previous history were obtainable—379 were new cases who had never undergone operative treatment; of these 201 (53·3%) were suitable cases for operation, while the remaining 178 (46·7 per cent.) were in too advanced a stage of the disease to permit of operative treatment.

Forty-eight were cases of recurrence who had had operations performed at other institutions, of these 41 had had one previous operation and 7 two; of the former it was found possible to perform a further operation in 4 cases, in the latter in 2 cases.

Of the new cases operated upon at the Middlesex Hospital (201), 67, i.e. 33·3 per cent. returned to the hospital at a later date with recurrence, and in the case of 31 were again submitted to operation. Of these 31 cases 12 returned a third time, an operation being carried out in 3 instances, one of these 3 cases again returning, and again being operated upon.

The percentage (33·3) of recurrences in cases operated upon at the Middlesex Hospital, by no means gives the true state of the case, as in the first place allowance has to be made for those cases (24) who died as an immediate consequence of the operative measures carried out (bringing the percentage up to 37·8 per cent.), and in the second place an indefinite proportion of operated cases are lost sight of by drifting to other hospitals and infirmaries.

Comparing this figure with that obtained in the case of cancer of the lip (18 per cent.), we find that recurrence is more than twice as common in cancer of the tongue. Deductions as to the relative frequency of recurrence in the two situations must not be too readily drawn, since the date after operation at which recurrence takes place is much later in the case of the lip than in the tongue, a fact which would allow of many of the cases moving away to other districts.

In the above figures males and females have been considered together, no material differences being found in the number of recurrences in the two sexes.

*Site of the Recurrent Growth.*—A study of 90 cases in which recurrence took place after operation shows that in 33 cases the mouth remained free from growth, in the remaining 57 cases the tongue, or both the tongue and cervical glands being affected. While in the majority of cases local recurrence showed itself either in the remaining portion of the tongue or in the operation scar, in 7 cases the second growth was stated to be *near* the scar of the operation, but not actually in it.

Out of 50 cases of cancer of the tongue dying in the Middlesex Hospital of recurrence, 22 (44 per cent.) were at the time of death free from any trace of growth within the mouth.

*Period after Operation at which Recurrence took place.*—In those cases (23) in which recurrence took place in the cervical glands alone the mean period after operation at which this showed itself was 7 months. In cases (35) where recurrence took place in the tongue or tongue and glands, the mean period was 6·4 months. This is excluding one case of abnormally long duration, in which the period before the second growth showed itself was 20 years.

### **Histology of Malignant Growths of the Tongue in General.**

Sections of primary tumours of the tongue have been preserved in 80 cases, and are available for collective investigation.

Of these 76 were squamous cell carcinomata, and the remaining 4 have already been fully described as endotheliomata, by Dr. Lazarus-Barlow in the third Cancer Report.\*

\* Arch. Middlesex Hosp., vol. iii., p. 74.

Of the squamous cell carcinomata there were 54 in which the arrangement of the cells may be regarded as typical, i.e. into three well-marked layers of cells—the Malpighian, the prickle, and the keratinising, which may or may not give rise to well-formed cell nests.

In the other 22 cases one or more of these layers was reduced, or so far as could be ascertained entirely absent. In 2 the tumour appeared to consist almost entirely of the Malpighian type of cell, while in 9 prickle cells were the chief constituent. In 10 cases the Malpighian layer was imperceptible; the tumour consisting of prickle and keratinising cells only.

No case was met with in which recurrent growths or metastatic growths in glands or viscera differed in any but the smallest details from the primary growth.

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# PRIMARY CANCER OF THE ŒSOPHAGUS AND LOWER PHARYNX: A STATISTICAL STUDY BASED ON THE RECORDS OF THE MIDDLESEX HOSPITAL.

By F. W. WRIGHT, M.R.C.S., L.S.A.

THE material dealt with in the following paper has been extracted from the records of the Middlesex Hospital for the fifty years—1855–1904. Although cases of œsophageal cancer are recorded in earlier years, they are so scanty, and the details are so sparse, that their inclusion was not thought advisable.

I.—The region dealt with in the present paper includes what is functionally the œsophagus, though anatomically it includes the pharynx below the level of the dorsum of the tongue, and behind the tonsils and soft palate. Such a limitation of the region is necessary for a convenient study of cancer of the upper part of the alimentary tract. Similarly, at the lower end it is not altogether possible to distinguish the lower end of the œsophagus from the cardiac orifice of the stomach when considering malignant disease.

II.—Two hundred and seventy-five examples of primary cancer of the œsophagus and lower pharynx are contained in the records of the Middlesex Hospital between the years 1855 and 1904, inclusive. Of this number (275) on 142 cases autopsies were made; on 25 cases no autopsies were made, though the patients died in the Hospital; and 108 cases were discharged from the Hospital.

III. **Incidence.**—(a) *Sex.* A great disparity is shown in the liability to the condition amongst males and females. Thus of 275 cases 230 occurred in males, and 45 in females; giving

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for males 83·6 per cent., and for females 16·4 per cent. It is to be noted, moreover, that more beds for cancer in the Hospital are apportioned to female cases.

(b) *Age.* The total average for both sexes was 53·1 years; the male average age was 54·2 years, and the female average age 47·3 years. The age was not given in the case of 8 males and 2 females.

Divided into quinquennial age periods the distribution of the remaining cases is as follows:—

Age-period.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.	80 to 84.
Males—											
Cases ...	2	5	14	30	39	61	40	22	8	—	1
Per cent. ...	·9	2·25	6·3	13·5	17·57	27·48	18·0	10·0	3·6	—	·4
Females—											
Cases ...	6	2	4	7	11	4	6	2	1	—	—
Per cent. ...	13·9	4·6	9·3	16·2	25·5	9·3	13·9	4·6	2·3	—	—

IV. *Duration.*—Taking all cases—including 14 with an abnormally long history—the total average duration of the disease was 7·4 months. By “abnormally long” cases are meant those in which the patient gave a history of from 2 to 15 years from the first sign of the disease. As such a duration is considered doubtful, and the inclusion of the cases in the total average duration of all examples is apt to be misleading, they are considered in a class by themselves; thus, the mean duration of the cases with an abnormally long history—14 in number—amounts to 4·5 years from the “first symptom.”

The average duration of the disease in the various classes is shown in the following table:—

TABLE I.

*The average duration of Primary Cancer of the Œsophagus and lower Pharynx from the first onset of Symptoms.*

	Months.
All cases . . . . .	7·6
„ „ dying in hospital . . . . .	6·9
„ discharged . . . . .	8·7

*Excluding 14 Abnormally Long Cases.*

All cases . . . . .	4·85
.. .. dying in hospital . . . . .	6·9
.. .. discharged . . . . .	1·31
All abnormally long cases alone . . . . .	54·0

From the above table it appears that the average duration of the disease from the first onset of symptoms is about 7 months.

V. **The "First Symptom."**—The symptom which the patient stated first drew his attention to ill-health in the cases under consideration, was recorded as being :—

Dysphagia, 166 cases; pain, 14 (epigastrium 7, back 1, lower sternum 2, clavicle 1, throat 3); "sore throat," 5; indigestion, 3; emaciation, 7; loss of appetite, 1; aphonia, 2; lump in throat, 1; cough, 3; vomiting, 9; enlarged glands, 1; bronchitis, 2; regurgitation of food, 1; nausea, 2; chilliness, 1; sense of lump in lower sternum, 1. Cases in which no first symptom is noted, 59.

VI. **The Chief Symptom.**—The chief symptom of primary carcinoma of the œsophagus and lower pharynx, as recognised on admission.

TABLE II.

	Cases.	Percentage.
Dysphagia . . . . .	172	61·4
Pain . . . . .	107	38·2
Regurgitation of food . . . . .	55	19·6
Vomiting . . . . .	69	24·6
Hæmorrhage . . . . .	11	3·9
Emaciation . . . . .	146	52·1
Aphonia . . . . .	15	5·3
Dyspnœa . . . . .	16	5·7

The prominent symptom, and the one which in the great majority of cases was the first to lead the patient to seek advice was *dysphagia*, with its 172 examples.

The next symptom in order of frequency was *emaciation*, with 146 instances. It was not as a rule an early symptom,

there being recorded only seven cases in which it led the patient first to seek advice, the remaining instances (139) either exciting no anxiety in the patient, or developing only in the later stages of the condition.

*Pain* was a marked feature in 107 cases. The chief seat of the pain was in the epigastrium (38 times). The character was in one case "burning," while in 9 it was excited by food. In 13 instances it was referred to the sternum, to the chest also 13 times, to the œsophagus 4, the back 4, below the clavicle 4, thyroid body 2, neck 2, throat 2, spinal column 2, liver 1, ear 1, posterior mediastinum 1, ribs 2 (in one from the first to the last, and in the other from the eighth to the eleventh inclusive), the shoulder 1, the cricoid cartilage 1, side 1, larynx 1. In 14 others it was noted but not located.

*Regurgitation* of food was noted in 55 cases, while vomiting occurred in 69.

It may be indicated here that a strict differentiation of these two symptoms has been observed; by regurgitation it is understood that the physical act of attempting to swallow caused the return of the food within a few seconds; and by vomiting is meant the rejection of the contents of the stomach independently of swallowing.

*Hæmorrhage* occurred in 11 cases, *Dyspnœa* in 16, and *Aphonia* in 15. In 2 of these it was a first symptom, while in 13 the condition developed at a later stage of the disease.

**VII. Occupation and Civil States.**—The occupations of the males (230) were as follows:—

*Males.*—Labourers, 34; carpenters, 12; painters, 13; bricklayers, 8; tailors, 14; shoemakers, 5; sailors, 4; travellers, 7; messengers, etc. 9; carmen, etc. 14; watchmen, shop, and warehouse, 24; publicans, etc. 13; various, 73.

*Females.*—(a) Occupations: Domestic servants, 7; nurses, 5; dressmakers, 4; housewives, or of no occupation, 29.

(b) Civil states: Of the 45 cases of females suffering from primary cancer of the œsophagus and lower pharynx there were married or widows, 32; single, 13.

**VIII. The Immediate Cause of Death.**—Of 134 cases in which autopsies were made, the immediate cause of death is given in 129.

They are tabulated as below :—

TABLE III.

*The Immediate Cause of Death in 134 cases of Primary Cancer of the Oesophagus and Lower Pharynx.*

Cause of Death.	Cases.	Percentage.
Malnutrition ... ..	42	31.3
Gangrene of lung ... ..	12	9.0
Broncho-pneumonia, simple... ..	16	11.9
"    "    septic ... ..	8	6.0
Hypostatic pneumonia ... ..	3	2.3
Edema of lung ... ..	3	2.3
Bronchitis and emphysema ... ..	11	8.3
Pleurisy ... ..	6	4.7
Perforation of pleura... ..	2	1.5
"    trachea ... ..	5	3.7
"    bronchus ... ..	3	2.3
"    posterior mediastinum ... ..	2	1.5
"    aorta ... ..	2	1.5
Hæmorrhage into stomach ... ..	3	2.3
Cerebral ... ..	2	1.5
Doubtful ... ..	14	10.6

**IX. The Secondary Growths.**—These are given in the following table :—

TABLE IV.

*The sites of Secondary Growths in cases of Primary Cancer of the Lower Pharynx and Oesophagus.*

	Recognised during Life, 280 Cases.	Recognised Post-mortem, 134 Cases.
Cervical and submaxillary glands ... ..	59	37
Bronchial and mediastinal glands ... ..	—	34
Oesophageal glands ... ..	—	6
Lumbar, iliac, and retro-peritoneal glands ... ..	3	10
Inguinal glands ... ..	2	—
Mesenteric glands ... ..	—	3
Sub-clavicular glands ... ..	1	4
Axillary glands ... ..	3	1
Thyroid ... ..	5	12
Thymus ... ..	1	—
Lungs and pleuræ ... ..	2	35
Pericardium ... ..	—	2
Heart—(a) auricle ... ..	—	2
(b) ventricle ... ..	—	1
Liver ... ..	6	15
Stomach and intestines ... ..	3	27
Peritoneum ... ..	1	23
Pancreas ... ..	1	2
Spleen ... ..	—	6



TABLE IV.—*continued.*

						Recognised during Life, 280 Cases.	Recognised Post-mortem, 134 Cases.
Kidneys	...	...	...	...	...	—	30
Adrenals	...	...	...	...	...	—	2
Tongue	...	...	...	...	...	1	1
Pharynx	...	...	...	...	...	2	2
Larynx	...	...	...	...	...	10	10
Brain—meninges	...	...	...	...	...	—	2
Abdominal wall at umbilicus	...	...	...	...	...	6	1
Skin	...	...	...	...	...	3	1
Vertebral column	...	...	...	...	...	1	6
Femur	...	...	...	...	...	1	1
Sternum	...	...	...	...	...	1	1
Ribs	...	...	...	...	...	3	—
With no secondary growths...	...	...	...	...	...	—	23

### X. The Primary Growth.

(a.) *Site.*—Situation of the primary growth opposite the bifurcation of the trachea claims the first place with 48 cases; at or just below the cricoid cartilage comes next with 36; the cardiac orifice of the stomach and up to 3 inches above it in the œsophageal tube follows with 35; in the middle third of this tract (using that term arbitrarily for convenience of description), 5; in the lower pharynx, 4; opposite the thyroid cartilage, 2; at the ary-epiglottic fold, 2; below the level of the vocal cords, 1; and opposite the thyroid lobes, 1.

(b) *The Character of the Growth.*—Hardness is noted as a prominent feature of the new growth in 54 cases; ulceration in 53; softness in 11; sloughing in 9; nodosity in 7; a papillomatous condition in 1. The “whiteness” of the growth was noted in 13 cases.

(c) *Extension of the Primary Growth.*—In considering the extension of primary cancer of the œsophagus and lower pharynx, proximity appears to govern the order of frequency, thus:—Extension towards the trachea occurred 29 times in a total of 120 cases in which the direction of the extension is recorded. Next in order of proximity and frequency are the bronchi, with 25 examples, in 15 of which perforation occurred; thus into the left bronchus there were 9 perforations; into the right bronchus, 2; into both bronchi, 2; in two cases there is no record in which bronchus it took place.

The pleural cavity shows extensions in 15 cases; and the tissue of the neck and mediastinum in 15. Towards the stomach there were 13 extensions, towards the vertebral column 6, towards the heart and aorta 6, the larynx 5, the thyroid 2, the pharynx 2, the liver 2. There were no extensions recorded in the remaining 14 cases.

The following table sets these data out in the order of their occurrence:—

TABLE V.

Direction of Extension.	Cases.	Out of a Total	Percentages.
(a) Towards the trachea ... ..	29	120	24·12
(b) " " bronchus ... ..	25	"	20·8
(c) " " pleural cavity ... ..	15	"	12·5
(d) Tissues of neck and mediastinum ... ..	15	"	12·5
(e) Towards the stomach ... ..	13	"	10·8
(f) " " vertebral column ... ..	6	"	5
(g) " " heart and aorta ... ..	6	"	5
(h) " " larynx ... ..	5	"	4·2
(i) " " thyroid ... ..	2	"	1·7
(j) " " liver ... ..	2	"	1·7
(k) " " pharynx ... ..	2	"	1·7
No extension recorded ... ..	14	134	10·4

*Heredity.*—The family history of the patient was recorded in 187 cases. Cancer occurred in near relatives of the patients in 16 instances, but in no case was the example one of primary cancer of the œsophagus or of the lower pharynx.

—	Cases.	Out of Total	Percentages.
Family history of cancer... ..	16	280	5·7
" " " absent ... ..	171	"	61·1
No record ... ..	93	"	33·2

**X. Operative Measures adopted in Primary Cancer of the Œsophagus and Lower Pharynx.**—These were undertaken in 49 cases:—Gastrostomy, 43; tracheotomy, 4; œsophagotomy, 1; double operations of tracheotomy and gastrostomy in the same patient, 1. All these means, which are clearly palliative only, appear to have afforded a certain amount of relief to the sufferings of the patients, and apparently

lengthened the lives of the majority. In the case in which œsophagotomy was performed, the patient survived the operation 19 days; while the mean duration of life of the 5 cases of tracheotomy after the operation was 38·85 days. The one case in which the double operation of gastrostomy and tracheotomy was performed on the same person at the same time lived 19 days.

**XI. Cases in which a Histological Examination was made.**—Histological examination of the primary and secondary growths was carried out on 28 of the 134 cases in which an autopsy was made. The microscopic diagnosis of these was as follows:—

Squamous cell carcinoma with cell nests . . .	17 cases.
Do., prickle cell type, no cell nests . . .	2 „
„ Malpighian and prickle cell type, no cell nests . . . . .	2 „
„ pure Malpighian cell type . . . . .	4 „
Columnar cell carcinoma . . . . .	3 „

In addition to the above the œsophagus was found to be secondarily the seat of carcinoma in 4 cases, the primary seats of the disease being cervix, larynx, tongue, and breast.

Metastases were found in 13 of the above 28 cases, in 4 of which the metastases were local, and confined to the lymphatic glands of the neighbourhood. In the remaining 9 they were widely spread, abdominal glands or viscera being involved in 6 cases.

# PRIMARY MALIGNANT DISEASE OF THE STOMACH: A STATISTICAL STUDY, BASED UPON THE RECORDS OF THE MIDDLESEX HOSPITAL.

BY HECTOR COLWELL, M.B.

THE pathological details for the present paper have been obtained from the post-mortem registers of the Middlesex Hospital from 1854 to 1904). These contain records of approximately 12,500 autopsies, of which 3,300 are cases of malignant disease. The present section deals with 227 cases of primary malignant disease of the stomach, which condition, therefore, accounts for 9·6 per cent. of the total autopsies upon cases of malignant disease. Although during the last five years of the above-mentioned period, regular histological examination has been the rule, this was not previously the case—or at least the results are not recorded—and, therefore, a separation into carcinomata and sarcomata is not attempted. In the section dealing with the histology of cases where the microscopic specimens are preserved, however, an account will be given of the situation of the primary growth, together with the distribution of metastases, and the age and sex of the patient.

The growths at present under consideration comprise those which have their primary seat between the cardiac orifice and the pyloric valve, although in some cases the œsophagus on the one hand, and the duodenum on the other, were found to be involved by direct extension. Considerable care was necessary to exclude growths primarily arising in the œsophagus. However, this source of error has been as far as possible avoided by the collaboration of Mr. Wright and myself. Primary new growth of the duodenum is so rare that error in this direction is negligible.

## PATHOLOGICAL DETAILS.

**Situations of the Growths.**—For purposes of classification, the growths are divided into three sections:—(1) Those arising either directly at the sphincter pylori or in the contracted

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portion of the stomach immediately adjacent to it, these are referred to under the heading of "Malignant Disease of the Pylorus." (2) Growths arising from the cardiac orifice or its immediate vicinity ("Malignant Disease of the Cardia"), and (3) Those growths which appeared to have their primary focus in any other part of the organ than those comprised under the first two headings ("Malignant Disease of the 'Body' of the Stomach").

**Relative Frequency of Sites.**—The pylorus was found to be the most frequently affected region, accounting for 149 cases of the 227, or 65·63 per cent; next in order comes the "body" of the stomach, with a total of 50 cases, or 25·99 per cent.; and lastly the cardia, with a total of 19, or 8·37 per cent.

**Sex and Age Incidence.**—Considering the stomach as a whole, the total number of males was 142 (62·56 per cent.), and of females 85 (37·44 per cent.); in other words the disease was found, post mortem, about 1·67 times as frequently in males as in females. Again, taking both males and females together, the general average age was found to be 50·9 years, the maximum recorded age being 75, and the minimum 20 years. The average age for males was 51·2 years, and for females 50·4. The maximum and minimum recorded ages being 71 and 22 years (males), and 75 and 20 years (females), respectively.

Moreover, when the age and sex incidence in the three regions of the stomach, mentioned above, are taken into consideration, there will be found in each case a numerical preponderance of males over females, and a greater average age for males than for females, as is shown in the accompanying table:—

TABLE I.

	Total Cases.	MALES.		FEMALES.	
		Number of Cases.	Average Age.	Number of Cases.	Average Age.
Pylorus ...	149	92 (61·7%)	51·4	57 (38·2%)	50·8
Body ...	59	37 (62·7%)	51·7	22 (37·3%)	49·4
Cardia ...	19	13 (68·9%)	49·0	6 (31·6%)	38·0



# MALIGNANT DISEASE OF THE STOMACH. 153

Considering the above figures, it will be seen that although the actual number of male cases increases with the total number of cases (male and female) as we pass from the cardia to the pylorus, yet the highest percentage of males occurs in malignant disease of the cardia, and the smallest in that of the pylorus. The small number of cases in which the cardia was the seat of growth may, of course, in part account for this.

The number of cases occurring in the various situations during successive quinquennial age periods, from 20 to 75 years, is shown in the following table. The patient, aged 20, was the subject of colloid spheroidal cell carcinoma of the pylorus (see No. 12 Table VI.).

TABLE II.

*Showing the Number of Cases of Malignant Disease of the Stomach in Different Situations, arranged in Quinquennial Age-Periods, from 20 to 75.*

Situation.	16 to 20.		21 to 25.		26 to 30.		31 to 35.		36 to 40.		41 to 45.		46 to 50.		51 to 55.		56 to 60.		61 to 65.		66 to 70.		71 to 75.	
	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.	M.	F.
Pylorus ...	—	1	1	1	2	1	2	5	6	6	13	7	21	3	18	11	11	5	12	11	4	4	2	2
Body ...	—	—	—	—	1	—	1	4	1	2	10	3	4	3	6	2	7	2	4	5	3	1	—	—
Cardia ...	—	—	—	—	—	—	—	1	5	—	1	2	—	—	1	1	4	—	2	1	—	1	—	—
Totals ...	—	1	1	1	3	1	3	10	12	8	24	12	25	6	25	14	22	7	18	17	7	6	2	2

## (A) MALIGNANT DISEASE OF THE PYLORUS.

These growths (149 cases) may be broadly divided into two groups. In the first class of case there is a complete, or almost complete, ring of growth, involving either the sphincter pylori itself, or the contracted portion of the stomach immediately adjacent. In the present series of cases a differentiation between those in which the sphincter itself was the primary focus, or the portion of stomach immediately adjacent, was not possible, as, in the first place the phrase "a mass of growth encircling the stomach at the pylorus" is not infrequently met with, especially in the older records; and in the second, a growth which was found at the autopsy to have encircled the pylorus, might have originated at a short distance therefrom. In the second class of case, however, this difficulty does not arise, as the malignant growth assumes the form of a localized tumour growing

from one aspect of the pyloric extremity of the stomach, and projecting more or less into its lumen.

(a) **Annular Growths.**—Cases of this description were 140 in number, or 93·9 per cent. of all malignant pyloric tumours examined. These, moreover, showed two different physical characters, for whereas 110 (78·6 per cent.) were described as “firm” or “hard,” 30 (21·4 per cent.) were described as “soft.” Though the latter condition may have been due in part to ulceration, this was certainly not always the case, as the firm growths were specifically described as “ulcerated” in 49 cases. Ulceration was present in 49 (44·5 per cent.) of the “firm” growths, and in 12 (40 per cent.) of the “soft.” Perforation occurred locally in 3 cases (·2 per cent.), causing fatal peritonitis.

Growths arising in this situation, however, are not always localized, but may extend either into the stomach itself, or into the duodenum.

*Extension into the Stomach Itself.*—This condition appears under two forms. In the first the whole circumference of the stomach may be uniformly infiltrated, this infiltration occupying, in some cases, what may be termed its “pyloric half.” Such extension was found in 25 cases (17·8 per cent.). Of these 25 cases, 20 were extensions from a pyloric growth described as “hard,” and 5 from a growth described as “soft.”

A second form of extension from the pylorus is that in which the small curvature alone is invaded to any extent; this occurred in 15 cases (10·7 per cent.), the pyloric growth being in all cases of the “hard” variety.

*Extension into the Duodenum.*—This was noticed in 13 cases (9·3 per cent.) of the series now under consideration. In 10 cases the pyloric growth was “hard,” and in 3 “soft.”

*Stenosis of the Pylorus* was observed in 94 cases (63 per cent.), varying in degree, from a constriction which was just perceptible, to one which merely admitted the passage of a probe. A “firm” pyloric growth was responsible for 60 out of these 94 cases (63·8 per cent.).

*Dilatation of the Stomach.*—Some degree of dilatation appears to have been almost universal; in 12 cases (8·6 per cent.) it was stated to have been “enormous.” Three cases however, with marked pyloric stenosis were described as

having the stomach "small." The latter cases did not present any marked extension beyond the localized growth at the pyloric extremity.

(b) **Polypoid Growths.**—The second variety of pyloric growth includes only 9 cases (6·7 per cent.), of which 6 occurred in males and 3 in females. A definite tumour projected into the cavity of the pyloric end of the stomach. In 5 cases (54·4 per cent.) it arose from the floor of the pylorus, in 3 (33 per cent.), from the posterior aspect, and in 1 from the upper aspect (11 per cent.). In all these cases there was definite dilatation of the stomach. The duodenum was not invaded in any case.

**Metastases and Extension.**—Metastatic deposits were observed in 115 cases (77·2 per cent.). The site of deposit and the number of cases in which deposits were found in each organ are set forth in Table IV. Direct extension had occurred into the liver in 23 cases, in 2 of which a cavity had been produced by ulceration, which communicated with the lumen of the pylorus and duodenum. In 5 of these cases there were no further hepatic deposits. In the case of the pancreas there were 16 instances of direct extension,\* but in 6 of these there were also secondary deposits. Of the growths producing no metastases, 34 in number, 22 were of the firm variety, 11 of the soft, and 1 a localized growth from the upper aspect of the pylorus.

## B) MALIGNANT DISEASE OF THE BODY OF THE STOMACH.

This was observed in 59 cases, and the situations of the various growths are detailed in the following table:—

TABLE III.

—						Males.	Females.
Small curvature	...	...	...	...	...	22 (37·3 %)	7 (11·8 %)
Diffuse infiltration	...	...	...	...	...	11 (18·6 %)	10 (17 %)
Posterior wall	...	...	...	...	...	1 (1·7 %)	1 (1·7 %)
Great curvature	...	...	...	...	...	2 (3·4 %)	2 (3·4 %)
Anterior wall	...	...	...	...	...	1 (1·7 %)	2 (3·4 %)
Total	...	...	...	...	...	37	22

\* This may be under-estimated because of the absence of histological examination in many cases. The respective colours of liver tissue and new growth render invasion microscopically evident.

**Malignant Disease of the Small Curvature.**—The small curvature, as seen above, accounts for 29 out of the 59 cases of malignant disease of the body of the stomach, i.e. 49·2 per cent. The disease was more or less limited to its site of origin in 53 cases (32 in males, 21 in females), but in 6 cases showed a tendency to invade adjacent parts of the stomach, extending to a considerable degree upon both anterior and posterior walls in 4 cases (3 males, 1 female), and in 2 cases (both males) involving the posterior wall alone to any great extent. As regards consistency, 15 of the growths were described as “firm,” and 14 as “soft.” Ulceration was present in 10 growths of the former character, and in 10 of the latter.

*Metastases.*—Of the 29 cases of malignant disease of the small curvature, 5 (17·2 per cent.) produced no metastases; 2 of these were of the “firm” and 3 of the “soft” variety.

**Diffuse Malignant Infiltration.**—Diffuse infiltration of the stomach by malignant growth, was noted in 21 cases (35·6 per cent.), of which 11 occurred in males and 10 in females; of these examples 14 were of firm consistency and 7 soft, and of the former 8 were so hard and dense that there was no tendency for the organ to collapse when opened in the post-mortem room. More or less ulceration was present in 6 cases, 4 being of the firm and 2 of the soft variety. Metastatic deposits were present in all but 2 instances, both of which occurred in males.

**Malignant Disease of the Posterior Wall.**—The posterior wall of the stomach was the primary seat of new growth in 2 cases (1 male, 1 female). In the case of the male subject (æet. 45), the growth was firm but ulcerated, and metastases were present in the portal glands and liver. Extensive bleeding had occurred into the stomach shortly before death, as the organ was described as “full of blood clot, which extended into the duodenum and jejunum.” The female patient showed a raised circular ulcer 1·75 inches in diameter, situated about the centre of the posterior wall, the growth was soft, centrally ulcerated, and adherent to and invading the pancreas. No secondary deposits were observed.

**Malignant Disease of the Great Curvature.**—The great curvature was the site of malignant disease in 4 cases (2 males, 2 females). In the 2 male cases it was firm, and in the



2 females soft. Ulceration was present in both the latter and in one of the former cases; metastases were present in all.

**Malignant Disease of the Anterior Wall.**—New growth had its origin in this locality in 3 cases (1 male, 2 female). In the 1 male case it was of soft consistency and metastases were present in the liver, pancreas, portal, aortic, and supra-clavicular glands. No ulceration was noted. In the 2 female cases, ulceration was present in both, one example being described as "firm" and the other as "soft." The firm growth produced no metastases, while the soft showed secondary deposits in the liver, and the portal, aortic, mesenteric, and mediastinal glands.

#### (C) MALIGNANT DISEASE OF THE CARDIA.

The records show only 19 examples of this condition (13 males, 6 females). In all cases the growth surrounded the cardia to a greater or less degree, and as in the two previously considered types of gastric new growth exhibited a difference of consistency. In 10 cases (53 per cent.) the growth was firm, and in 9 cases (47 per cent.) soft. Of the 10 former cases, 7 occurred in males and 3 in females, and 6 were the seat of ulceration. The 9 soft growths in 3 cases occurred in females and in 6 in males. Only 1 definitely polypose growth was noted. This was of hard consistency and produced metastases in the portal glands. In 2 cases only were no metastases described; both growths were of the soft variety, 1 occurring in a male and 1 in a female. The lower end of the œsophagus was invaded in 2 cases, both of which showed also isolated metastases a short distance above the cardiac orifice.

TABLE IV.

*Showing Sites of Metastatic Deposits (apart from Extensions) in 227 Cases of Malignant Disease of the Stomach.*

Site.	Pylorus.	Body.	Cardia.
Cerebellum ...	—	—	1
Lung ...	5	3	2
Pleura ...	5	4	1
Pericardium ...	1	1	—
Heart ...	2	—	1
Liver ...	47	27	12
Pancreas ...	6	4	3



TABLE IV.—*continued.*

Site.					Pylorus.	Body.	Cardia.
Esophagus ...	...	...	...	...	—	—	2
Stomach ...	...	...	...	...	5	4	2
Intestine ...	...	...	...	...	1	—	1
Spleen ...	...	...	...	...	1	—	2
Adrenals ...	...	...	...	...	3	—	5
Kidneys ...	...	...	...	...	2	1	1
Ovaries ...	...	...	...	...	3	2	—
Peritoneum ...	...	...	...	...	29	21	2
Thoracic duct ...	...	...	...	...	1	1	—
Portal ...	...	...	...	...	50	27	3
Cœliac ...	...	...	...	...	30	12	4
Aortic ...	...	...	...	...	20	20	8
Lymphatic Glands, Inguinal ...	...	...	...	...	—	1	—
Mediastinal ...	...	...	...	...	3	4	6
Mesenteric ...	...	...	...	...	25	15	5
Axillary ...	...	...	...	...	1	—	—
Supra-clavicular ...	...	...	...	...	—	1	—
Ribs ...	...	...	...	...	1	1	—
Vertebrae ...	...	...	...	...	1	—	1
Humerus ...	...	...	...	...	—	1	—
Sacrum ...	...	...	...	...	—	1	—
Skin ...	...	...	...	...	1	—	2

## HISTOLOGY.

Of the 227 autopsies dealt with, histological examination was made in 53 cases, or 23·3 per cent., and it is a remarkable fact that this high percentage of the total should have come under observation during the years 1900–1904 inclusive. By reference to the accompanying table it will be seen that carcinoma accounts for 48 out of the 53 cases (90·5 per cent.), and sarcoma for only 5 (9·4 per cent.).

The carcinomatous growths (considering the stomach as a whole) show the following totals and percentages for spheroidal, columnar, and squamous cell carcinomata. Spheroidal cell 30 (62·5 per cent.), columnar cell 17 (35·4 per cent.), and squamous cell 1 (2 per cent.) respectively. Further, of these 48 cases of carcinoma, 28 (58·3 per cent.) occurred in males and 20 (41·7 per cent.) in females. Of the 28 male cases 18 (64·3 per cent.), and of the 20 female, 12 (60 per cent.) were cases of spheroidal cell carcinoma. Columnar cell carcinoma was found in 17 cases of the 48, 9 males (53·5 per cent.) and 8 females (46·5 per cent.) Passing now to the 3 regions of the stomach, namely, pylorus, body, and cardia, it is found,

that of 27 cases of pyloric carcinoma, 16 (59·3 per cent.) were of the spheroidal, as against 10 (37 per cent.) of the columnar and 1 of the squamous (3·7 per cent.) variety.

The "body" of the stomach was the site of a spheroidal cell growth in 13 (65 per cent.) of the 20 cases in which this region was affected, as against 7 (35 per cent.) in which the growth was of the columnar cell variety.

The 1 case of carcinoma at the cardia, of which the histology is available, was of the spheroidal cell variety.

The following table sets forth the previously mentioned relations. Of course the number of cases considered under "cardia" and "squamous cell" carcinoma are too small to be of value, they are merely added to complete the table.

TABLE V.

*Table showing the Percentage Occurrence of the different varieties of Carcinoma in the various regions of the Stomach and in the two Sexes.*

Type of Carcinoma.	Whole Stomach.	Pylorus.	Body.	Cardia.	Percentage in Sexes.	
					Male.	Female.
Spheroidal cell ...	62·5 %	59·3 %	65 %	100 %	58·3 %	41·7 %
Columnar cell ...	35·4 %	37·0 %	35 %	—	53·5 %	46·5 %
Squamous cell ...	2·0 %	3·7 %	—	—	100	—

The sarcomata are obviously too few in number for any attempt at generalization.

TABLE VI.

*Showing situation of Primary Growth and Metastases in fifty-three cases of Primary Malignant Disease of the Stomach.*

## CARCINOMATA.

—	Initials, Age, Sex.	Character of Growth.		Metastases.
Pylorus.				
1	A. C. m. 53...	Columnar,	becoming	Liver, lungs, mesenteric glands.
2	E. F. f. 57 ...	transitional	... ..	Peritoneum, mesenteric, and aortic glands.
3	M. G. f. 70 ...	Columnar	... ..	Peritoneum.
4	H. W. m. 64	Columnar,	becoming	None.
5	D. O'G. m. 35	transitional	... ..	Portal glands.
6	G. B. m. 55...	Columnar,	becoming	Liver, aortic glands
		transitional	... ..	

## 160 MALIGNANT DISEASE OF THE STOMACH.

TABLE VI.—*continued.*

	Initials. Age, Sex.	Character of Growth.		Metastases.
Pylorus.				
7	A. F. f. 69 ...	Columnar,	becoming transitional	None.
8	W. H. S. m. 66	Columnar	... ..	Celiac glands.
9	E. M. f. 53 ...	Columnar,	becoming transitional	Liver, pancreas, glands.
10	E. W. m. 59	Columnar	(simulating Perithelioma)	Liver, kidney, adrenal, portal glands, thoracic duct.
11	J. E. m. 54 ...	Spheroidal	... ..	Liver, lung, mesenteric glands.
12	J. B. f. 20 ...	Spheroidal (Colloid)	... ..	Lung, peritoneum, media- stinal and aortic glands.
13	E. E. f. 35 ...	Spheroidal	... ..	Lung, ovary.
14	J. H. f. 50 ...	Spheroidal (Colloid)	... ..	Peritoneum.
15	S. E. m. 66...	Spheroidal	... ..	None.
16	E. L. f. 59 ...	"	... ..	Stomach, aortic glands.
17	M. E. H. f. 40	"	... ..	Adrenals, glands.
18	W. E. m. 70	"	... ..	Peritoneum.
19	A. S. m. 30 ...	"	... ..	Liver, glands.
20	G. B. m. 50...	"	... ..	None.
21	E. B. f. 64 ...	"	... ..	None.
22	J. B. m. 38 ...	"	... ..	Liver, spleen, glands.
23	J. F. m. 57 ...	"	... ..	None.
24	M. McL. f. 35	"	... ..	Liver, abdominal wall, glands.
25	J. D. m. 63...	"	... ..	Stomach, peritoneum.
26	E. V. f. 64 ...	Spheroidal (Colloid)	... ..	Peritoneum.
27	W. W. m. 45	Squamous	... ..	Peritoneum.
Body of Stomach.				
28	A. W. f. 48...	Columnar,	becoming transitional	Glands.
29	M. G. f. 63 ...	Columnar,	becoming transitional	None.
30	S. D. f. 64 ...	Columnar	... ..	Stomach, portal glands, liver.
31	W. C. m. 45	Columnar,	becoming transitional	None.
32	B. F. f. 61 ...	Columnar	... ..	Liver.
33	W. A. m. 67	"	... ..	None.
34	E. G. m. 63...	"	... ..	None.
35	F. S. m. 60 ...	Spheroidal	... ..	Liver, celiac glands.
36	W. M. m. 61	"	... ..	None.
37	R. T. m. 61...	"	... ..	Celiac glands.
38	E. B. f. 62 ...	"	... ..	None.
39	E. A. m. 57...	"	... ..	Liver, adrenal, glands.
40	T. R. m. 50...	"	... ..	Kidney, glands.
41	E. B. f. 31 ...	"	... ..	Liver, lung, glands.
42	F. B. m. 45...	"	(Colloid) ...	Liver, peritoneum.
43	W. N. m. 55	"	... ..	Liver, peritoneum.
44	A. H. m. 43	"	... ..	Pericardium, pleura, peri- toneum, celiac glands.
45	W. F. m. 57	"	... ..	Liver, peritoneum, glands.
46	M. M. f. 34 ...	"	... ..	Liver, ovaries.
47	M. L. f. 56 ...	"	... ..	Liver.
Cardia.				
48	T. D. m. 40...	"	... ..	Liver, pancreas, aortic glands.

TABLE VI.—*continued*.  
SARCOMATA.

—	Initials, Age, Sex.	Character of Growth.	Metastases.
Pylorus.			
1	J. H. m. 41...	Mixed cell ... ..	None.
2	D. H. m. 60...	" " ... ..	Coeliac glands, peritoneum.
3	J. P. m. 38...	Small round cell ...	None.
Body of Stomach.			
4	A. P. m. 52...	Mixed cell ... ..	None.
5	R. A. C. f. 54	Spindle cell ... ..	None.

## CLINICAL DETAILS.

Although notes of cases from 1746 to the present time are extant at the Middlesex Hospital, no case of "cancer of the stomach" is recorded prior to 1815. The clinical details, moreover, previous to 1875 are scanty in respect to their accounts of the somewhat complicated symptoms of lesions of internal organs; although, in many instances, the signs of disease in superficial organs, such as the breast or lip, or of organs accessible to digital examination, such as the uterus, are detailed with sufficient accuracy to warrant their inclusion in a statistical paper. For this reason, the observations upon the clinical manifestations of malignant disease of the stomach will be confined to the period 1875–1904. Operation cases will be considered under the clinical aspect of the case, as in most instances operative procedure appeared to be resorted to, not for diagnostic purposes, but for the relief of symptoms due to a previously diagnosed condition. Further, in the case of an operation, the description of the growth cannot be given with the same exactness as when the organ is removed and opened at an autopsy; small metastases similarly, would not be so carefully sought at an operation. A further advantage of such a separation of cases, is, that in considering autopsy cases together, we are considering a homogeneous series in which a complete and thorough examination of all organs has been made.

Between the years 1875 and 1904, 295 cases were diagnosed as malignant disease of the stomach, including those verified by autopsy or operation. The males numbered 175, the females 120.

The average age of all cases admitted during that period was 52·3 years; of males 53·6 years, and of females 51·8 years.

### Initial Symptoms.

In the 278 cases in which these details are available, co-existing pain and vomiting were the most frequent initial symptoms, being recorded in 92 cases or 31·2 per cent.

The next most frequent initial symptom is pain alone (80 cases or 27·1 per cent.). Vomiting apart from pain comes third upon the list, and was recorded as the initial symptom in 73 cases (25 per cent.). Among other initial symptoms are mentioned, emaciation in 19 cases, and co-existing pain and emaciation in 13 cases. Jaundice was the first symptom noted in 1 case, it was found post mortem to be due to the pressure of cancerous glands (secondary to malignant disease of the pylorus) in the portal fissure of the liver. Vomiting almost always appeared at first after feeding, and gradually increased in frequency towards the end of the disease, when it was in most cases almost constant. In 11 cases, the vomiting appeared to manifest itself in the first instance at night, but subsequently occurred in the day-time and continued with increasing frequency. In the earlier stages it appeared to be associated with the ingestion of solid food, so that before presenting themselves at the Hospital many patients had found it necessary to have recourse to a "slop" diet. In 12 cases vomiting appears to have been absent, or only appeared quite in the last stages of the illness.

Pain was likewise absent in 13 cases, though present in the rest. Like vomiting it usually at first appeared after solid food, its onset varying from a few minutes to three hours after the food had been taken. Subsequently in the majority of cases, pain, like vomiting, became a more constant feature, though subject to considerable exacerbation after food (especially solids). In 26 cases, however, the pain did not appear to present any definite relation to meals, but came on at varying times; in 25 cases it was explicitly stated to be worst at night. When pain occurred after food it appeared to be nearly always relieved by vomiting.

Six patients, in whom malignant disease of the stomach was found post mortem, presented no symptoms of the con-



dition during life, and were admitted for other ailments. One interesting case in this connection is that of a woman admitted to the "Cancer Wing" of the hospital; she presented no gastric symptoms whatever, yet, at the autopsy, diffuse (spheroidal cell) carcinoma of the stomach was found. She had been admitted for malignant disease of both ovaries, but this, although verified by the post-mortem examination, was found to be secondary to the gastric lesion.

A palpable abdominal tumour was noticed in 227 cases (81·6 per cent.) of the 278 where the notes are available. It was described as situated in the "epigastric" region in 101 cases (44·5 per cent.); in the "umbilical" in 43 (18·9 per cent.); in the right hypochondrium in 52 (22·4 per cent.); in the epigastric and umbilical regions in 12 (5·2 per cent.); in the epigastric and right hypochondriac in 12 (5·2 per cent.); and in the umbilical and right hypochondriac regions in 7 cases (3 per cent.). In 12 cases (5·2 per cent.) the tumour was found to be movable, shifting in position day to day, 5 of these 12 cases were subsequently verified post mortem as malignant disease of the pylorus. In the case of persons dying with malignant disease of the cardia, no record obtains of a palpable tumour. Those with malignant disease of the body of the stomach showed a palpable tumour in 42 of the 48 cases of that condition which were examined post mortem between 1875 and 1904: the swelling was in the following situations, epigastrium 20 cases; umbilical region 19; umbilical and epigastric regions 3. Finally, of 112 cases of pyloric malignant disease verified post mortem during the same period 87 exhibited a palpable tumour during life, situated in the epigastric region in 39 cases; in the right hypochondrium in 33; in the epigastrium and right hypochondrium in 8; and in the umbilical and right hypochondriac regions in 7 cases.

Abdominal tenderness was noted in 243 out of 278 cases. Of the 35 cases in which it was absent 11 presented a palpable tumour. The other cases in which such a tumour was present presented more or less tenderness over the situation of the tumour.

*Hæmorrhage.*—Definite hæmatemesis was recorded in 15 cases, and co-existing melæna in 6. "Coffee ground" vomit, apart from definite hæmatemesis was observed in 21 cases, and

melæna was reported apart from other obvious manifestations of hæmorrhage in 4 cases.

Emaciation was present to a greater or less extent in 257 out of 278 cases, the remaining 21 cases being described as "well-nourished."

*Duration of the Disease.*—The average duration of the disease (calculated from 197 cases where the date of onset was given with sufficient accuracy) from the onset of the first symptom till death was 6·7 months, the minimum period being 1 month, and the maximum 16 months. In 17 out of 278 cases, it was specifically stated that the patient had "always suffered from indigestion," and in 173 there was a history of flatulence, pyrosis and minor digestive disturbances for varying periods before the onset of any very distressing symptom.

Alcoholic excess is mentioned in 47 (16·85 per cent.) of the 278 cases whose clinical notes are available. The character of the liquor taken was frequently not mentioned, but 14 are stated to have used beer and spirits freely.

**Operative Measures.**—Under this heading, only the number of operations and their character can be considered, as, in the cases which become convalescent, the patients leave hospital and no further history of their progress is available from the materials at our disposal. One case, however (of gastro-jejunostomy), survived the operation sixteen months and eventually died in the Cancer Wing. The numbers of the various operations are as follow:—"Gastro-jejunostomy" 22, "gastro-enterostomy" 4, "gastro-duodenostomy" 5, "gastrostomy" 2, and "pylorectomy" 2, "laparatomy" is mentioned 8 times, but in how many of these cases the operation was exploratory, and in how many merely the initial step in a contemplated more radical operation, cannot be said.

*Occupation.*—The occupations quoted below represent those of the 175 male patients at the time of their admission to Hospital:—

Woodworkers 17; Upholsterers 5; Painters, Decorators, etc., 13; Labourers 11; Tailors 6; Bootmakers 7; Travellers 5; Porters and Messengers 14; Gardeners 4; Bakers 3; Metalworkers 14; Builders, Bricklayers, and Masons 14; Stablemen, etc., 17; Shopmen 10; Cooks 1; Barmen 2; Clerks, etc., 12; Various 23.

# CANCER OF THE UTERUS, VAGINA, AND VULVA; A STATISTICAL STUDY OF THE RECORDS OF THE MIDDLESEX HOSPITAL.

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IN the following pages a statistical account is given of 2,347 cases of malignant disease of the uterus, vagina, and vulva, the records of which are preserved at the Middlesex Hospital. The series includes all cases of cancer of these organs occurring in the practice of the Hospital from 1855 to 1904, together with 13 cases occurring between 1808 and 1818; before the early period, and between the two, the meagre records do not contribute anything to an analysis. The cases are divided into sections according to the primary site of the disease and, further, cancer of the uterus itself is sub-divided according as it affects the cervix or the corpus.

Since the number of cases of cancer in females recorded from 1855 till 1904 is 5,359, cancer of the uterus, vagina, and vulva, constitute, according to the experience of this Hospital, 43·6 per cent. of all malignant disease in women, while cancer of the cervix alone (2,111 cases) accounts for nearly 40 per cent. of all female cancer and for over 90 per cent. of all malignant disease of the female generative organs, cancer of the ovaries and Fallopian tubes being so rare as to be negligible in the present consideration.

As in the case of other statistical papers on cancer at different sites contained in the present and preceding reports from these laboratories, all the cases were not available for every point that was investigated; the number of cases, however, on which any percentage is based is always given.

At the end of each section will be found a brief account of the histology of such cases as have been admitted to the

Hospital, and have either died there or undergone operation since the year 1900; of all such cases the histological sections are preserved along with sections of any metastases that may have been present. In all, 185 cases are available for a consideration of the histological characters of the growths, viz., cervix, 151; body of the uterus, 16; vagina, 6; and vulva, 12.

## I.—MALIGNANT DISEASE OF THE CERVIX UTERI.

### GENERAL DETAILS.

**Civil Condition and Fertility.**—Of 1,876 cases, cancer of the cervix occurred in 1,790 married women, and in 86 unmarried (4·59 per cent.), that is to say, it is twenty times as common in the former as in the latter. In the general population the proportion of married to unmarried of the adult female population is about 5:1. The disparity is striking.

Of the cases considered 1,403 had given birth to one or more children, 22 had been pregnant but had never produced full-term or living children, but merely abortions, and 127 (9 per cent.) were sterile though married.

**Heredity.**—In recording the family histories in cancer cases in the Middlesex Hospital, special attention has always been paid to the presence or absence of cancerous or phthisical taint. Among 1,500 cases so recorded, 789, or 52·6 per cent. were free from cancer or phthisis, 557, or 37·13 per cent., gave a history of phthisis, and 242 (16·13 per cent.) one of cancer. In 88 (5·9 per cent.) there was a history of phthisis and cancer.

*Homologous Heredity.*—83 cases, or 5·5 per cent. of the total, gave a family history of uterine cancer; the mother was affected in 44 (2·9 per cent.), a sister in 27 (1·8 per cent.), an aunt in 15 (1 per cent.), and the maternal grandmother in 7 (0·41 per cent.).

**Cancer à Deux.**—In 7 cases there was a history of cancer in both husband and wife, representing a percentage of about 0·5. The distribution of cancer in the husbands was as follows: Stomach 2, liver 1, tongue 1, penis 1, and locality unstated in 2. In the case of the stomach cancer the husband died six months after the patient herself was affected, and in



the case of the penile cancer the husband had died seven years before the onset of the patient's own symptoms.

**Age at Onset.**—The age at onset of the disease was estimated by subtracting the duration of the cardinal signs and symptoms—pelvic pain, hæmorrhage, and vaginal discharge—from the age of the patient on admission. In those cases where a single symptom was separated by an inordinate length of time from the others, the single symptom was ignored in making this calculation. The age at onset was thus approximately determined in 1,639 cases. The duration was calculated not in months but in the approximate quarters, and the age given by the patients was taken as if an exact one on the date of admission, a source of fallacy which will render the average age at onset in the calculation inaccurate by an unknown fraction of a year. Nevertheless the number of cases considered eliminates from the averages the errors of particular over- and under-estimations. The mean age at onset is 44·63 years. The oldest patient had an onset age of 86·5, and the youngest 22. The average age at onset among the unmarried was found to be 43·85, but the smallness of the number of cases from which it was calculated (47) renders the slightly earlier onset of no comparative importance.

*Table showing the number of Cases of Cancer of the Cervix commencing during the various Quinquennial Age Periods.*

Age {	20 to 24.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.	80 to 84.	85 to 89.
No. of cases ...	6	85	167	305	319	289	205	136	89	23	11	3	—	1
Percentage ...	0·37	5·19	10·19	18·61	19·46	17·63	12·51	8·30	5·43	1·40	0·67	0·18	—	0·06

**Onset in Relation to Menopause.**—This was mostly calculated directly from cases in which the time of the cessation of menses was supplied or where the continuance of the flow was recorded, but a few cases were reckoned relatively to the mean menopause age of 45·5 years—obtained by taking the average of 566 cases. The result is that 894 cases, or 51 per cent., were found to occur before the menopause; 655, or 40 per cent., after; while 90, or 9 per cent., had an advent inseparably blended with its phenomena.



**Onset in Relation to Pregnancy.**—From 947 cases where particulars regarding the onset of the disease and the time of the last pregnancy or abortion are supplied, it is estimated that 103, or 10·9 per cent., bear a close relation to pregnancy. More particularly, the onset of symptoms of cancer of the cervix preceded abortion or live birth in 17 cases (1·8 per cent.); they were present during the later stages of gestation, during the puerperium, or at the time of abortion, in 32 instances (3·4 per cent.); in 43 cases (4·5 per cent.) the onset of symptoms dated from the puerperium; and in an additional 1·2 per cent. (11 cases) less than six months had elapsed between birth or abortion and the commencement of the disease. Not only is cancer of the cervix not a bar to successful natural delivery, but it does not prevent conception. One woman, who was an in-patient of the Middlesex Hospital suffering from cancer of the cervix was discharged, was delivered with forceps of a live full-term child at another hospital about a year afterwards, and was readmitted to this Hospital.

**Relation to the Menstrual Function.**—*Onset of the Catamenia.*—The average age at which the menses started, calculated from a total of 1,070 cases, was 14·35. The following table shows the distribution according to the year of onset:—

Age	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Number of cases ...	1	—	20	74	104	165	214	202	135	82	46	15	10	2

**Periodicity of the Menses.**—Calculating from 216 cases, the menses recurred at intervals of four weeks or a month in 181 (83·8 per cent.), three-weekly in 25 (11·6 per cent.), fortnightly in 7 (3·2 per cent.), weekly in 1 (0·5 per cent.), and at intervals of six to seven weeks in 2 (0·9 per cent.). The patient that menstruated weekly was unmarried; the menstrual flow lasted two days at a time.

**Duration of the Menstrual Flow.**—Particulars regarding this point are given in 114 cases—

14 days	.	.	.	.	2 cases	1·75 per cent.
8	„	.	.	.	4 „	3·5 „ „
7	„	.	.	.	23 „	20·2 „ „

6 days . . . . .	19 cases	16·4	per cent.
5 .. . . .	21 ..	18·7	.. ..
4 .. . . .	26 ..	22·8	.. ..
3 .. . . .	17 ..	14·9	.. ..
2 .. . . .	2 ..	1·75	.. ..

*Regularity of the Menses.*—Of 1,232 cases, 1,161, or 94·2 per cent. were regular and 71 or 5·8 per cent. were irregular as to the recurrence of the menses.

*Quantity of Blood lost during the Flow.*—56 cases had a scanty loss, and in 77 menstruation was profuse. There is no criterion in the records by which to judge the frequency of these deviations from the ordinary, but taking as a standard of comparison the number in which the recurrence of the flow was stated to be regular, namely, 1,161, about 5 per cent. were “scanty” and 7 per cent. were “profuse.”

*Cessation of the Menses.*—Taking the average of 566 cases where the time of cessation of the menses is recorded, the menopause occurred at the age of 45·5 years. Eliminating those cases in which the menses ceased before the age of 40 was attained as not giving a true menopause, the mean menopause age arrived at from 493 cases is 46·9 years—an estimation of 0·6 of a year lower than that of Mr. Ball in the present volume of the Archives. The general opinion that the earlier menstruation commences the earlier does the menopause occur, or that the later the one the later the other, is not borne out in this analysis; a longer duration of sexual life is, however, noted in those who commence to menstruate before the age of 17.

Age at which } Menses began }	10	11	12	13	14	15	16	17	18	19	20	21
Average age at } Menopause }	40·9	46·2	44·7	44·4	45·6	45·5	46·7	45·9	45·6	47·1	48·8	45
Mean duration of } Sexual Life }	39·9	35·2	32·7	31·4	31·6	30·5	30·7	28·9	27·6	28·1	28·8	24

*Duration.*—By adding the duration of the disease before admission to the length of time that elapsed between admission and death, omitting those cases in which a surgical operation of any importance affected the natural evolution, and reckoning in approximate quarters, we obtain the

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approximate duration of the disease in 900 cases. From the appearance of the first symptom till the time of death the shortest duration was 3 months and the longest 7 years. The average duration is 1·74 years, or 1 year and 9 months.

*Table showing the Average Duration, in years, during the various Quinquennial Age Periods and the Number of Cases in each from which Calculations were made.*

Age {	20	25	30	35	40	45	50	55	60	65	70	75
	to 24.	to 29.	to 34.	to 39.	to 44.	to 49.	to 54.	to 59.	to 64.	to 69.	to 74.	to 79.
Number of cases	4	45	90	162	161	155	119	72	65	16	8	3
Mean duration of disease }	1	1·35	1·45	1·59	1·60	1·69	1·95	1·88	2·27	2·06	1·75	0·92

Thus the duration of the disease increases gradually (excepting a slight retrogression during the quinquennial period 55-59) with the age of the patient, until it reaches its maximum between the ages of 60 and 64, thence it diminishes quickly to its minimum during the age period of 75-79.

### CLINICAL DETAILS.

Considering the widely different stages of the disease at which patients presented themselves and the various estimations which different observers naturally attach to each symptom, it is impossible to record in accurate percentages the comparative presence or absence of such. It is also to be remembered that of those patients whose progress was watched from beginning to end, in view of the hopeless prognosis of the observer, the nearer the fatal issue the less minute would be the search for a symptom or a sign more or less. The figures at most can only convey a rough impression of the relative frequency with which each symptom is encountered.

**Pain.**—This is noted as being present in 1,423 cases and definitely absent in 73; while of cases that subsequently came to post-mortem examination, and of which, therefore, the terminal history is known, no record of the presence of pain either on admission or at any time up to death was found in

19 cases. The estimation that 5 per cent. of cases experienced no pain is probably an over-statement, but whatever the magnitude of the error may be, it seems probable that there are some cases in which pain is absent when the disease is fairly well established, and some even which do not suffer pain at all during its whole course.

**Hæmorrhage.**—The occurrence of abnormal vaginal hæmorrhage is recorded in 1,374 cases, and its absence in 73 or 5 per cent. Of cases in which the terminal history is known there was no note of its appearance in 19.

**Discharge.**—Vaginal discharges other than hæmorrhage, described as watery, purulent, and offensive, were noted in 1,339 cases, and absent in 26 or 2 per cent. The discharge was definitely described as offensive or foul-smelling in 582 instances.

**Emaciation.**—In the cases where we have to depend on the clinical records alone, emaciation is recorded as present in 469 cases and absent in 70 (13 per cent.). In many cases the emaciation is only a relative term in consideration of the patient's previous state, and is probably more accurately expressed in their own words as "loss of flesh," but the pathologist's use of the term is a more absolute one. In 915 post-mortem records, emaciation is absent in 175, that is in 19.1 per cent. Of these latter, 26 had visceral metastases, i.e. 14.86 per cent.

**Troubles of Micturition.**—The troubles of micturition, including difficulty, pain or smarting during the act, retention, frequent desire, frequency, and incontinence, are most easily included under one heading for they are, one or more, most often combined, or but different stages in the course of the affection. Such abnormalities were present in 542 cases and absent in 84.

**Fistulæ.**—Among the clinical records alone, 1,038 cases were considered of sufficient general excellence as to afford evidence on this head. 36 cases showed a fistulous communication between the vagina and the bladder (3 per cent); 19 cases a communication between the vagina and rectum (1.5 per cent); double fistulæ, that is communications between the vagina, bladder, and rectum, were recorded in 6 cases, or in about 0.5 per cent.



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Among the 915 post mortems, 404 (44·2 per cent.) had a vesico-vaginal opening, 151 (16·5 per cent.) a communication with the rectum, while 86 or 9·4 per cent. had double fistulae.

**Involvement of the Vagina.**—In those cases in which the clinical record alone is available, the vagina was involved by the spread of the malignant process in 449 cases and uninvolvement in 40 (9 per cent.). The post-mortem records in 847 cases give the vagina as being involved in 826 and not affected in 21 (2·5 per cent.).

**Enlargement of the Uterus.**—Among the 1,040 purely clinical cases the uterus is noted as being enlarged in 148. This is from information gathered by bimanual examination alone, and does not necessarily imply that the enlargement was due to the spread of the malignant growth nor that in those cases where it was not so recorded there was no such involvement of the uterine body. Malignant affection of the uterine body will be considered later, under the heading of Local Spread.

**Fixation of the Uterus.**—Particulars regarding this are supplied in 676 cases; it was present in 578 (85·5 per cent.), and absent in 98 (14·5 per cent.).

**Gastro-intestinal Derangements.**—There were 636 cases giving information under this heading.

Gastric disturbances, such as anorexia, sickness, nausea, and vomiting, were recorded in 343 instances or 54 per cent.

Pain or difficulty in defæcation was noted in 152 cases (24 per cent.).

These percentages are hesitatingly given, for the notes vary considerably in the attention paid to such symptoms and rarely definitely record their absence.

**Other Clinical Facts.**—Insanity developed during the course of the disease in 17 cases. Old-standing leucorrhœa was complained of in 53 cases and "inflammation" or "ulcer of the womb" in 31. 18 patients had had previous syphilis and 2 gonorrhœa. In 16 cases there was prolapsus uteri, 6 of whom had worn pessaries for its relief.

Cæsarian section had to be performed on two of the patients owing to the obstruction caused by the cervical tumour; the first case was recorded in 1865. Five patients had previously had a breast removed for cancer of that organ.

Of 1,000 clinical histories, previous operation for fibroids were recorded in 6. Cancer of the cervix occurred in one patient the subject of hamophilia, and in another the subject of myxœdema.

#### PATHOLOGICAL DETAILS.

**Site of the Growth.**—In the great majority of the cases no attempt can be made to localize the exact position in the cervix from which the growth started. The following parts were principally or solely affected: endocervix in 30 per cent., anterior lip in 20 per cent., posterior lip in 45 per cent., right side in 1 per cent., and left side in 4 per cent., an estimation based on the records of 137 cases mainly clinical but partly post mortem.

**Ulceration.**—At the first examination of the patient, in 802 cases the growth was ulcerated, and in 26 or 3·14 per cent. ulceration had not commenced, nevertheless in only one case out of the 915 autopsies was ulceration absent.

**Local Spread.**—The records of the post-mortem examinations show that in 32 cases (3·5 per cent.), the disease had not spread beyond the cervix nor had any metastatic deposits occurred.

**Body of the Uterus.**—The corpus was involved in the spread of the malignant process in 613 cases and not involved in 83 or 10·9 per cent. In 219 cases there was no note on the point.

**Vagina.**—The vagina is recorded as being involved at post-mortem examination in 826 cases and uninvolved in 21 (2·5 per cent. In 68 cases there was no note on the point.

**Bladder.**—In addition to the numbers given before for fistulous communications with the bladder the walls of that viscus were involved without perforation in 204 cases on which post-mortem examination was performed. Altogether the bladder was involved in 608 cases and unaffected in 77 (11·3 per cent.). In 230 cases there was no note on the point.

**Rectum.**—In addition to the number given for recto-vaginal perforations the rectum was involved without perforation in 98 post-mortem cases, making a total of 249. The rectum was free from involvement in 48 instances (16·2 per cent.). In 618 cases there was no note on the point.

**Vulva.**—Involvement of the vulva by a continuation of the malignant process from the cervix through the vagina is recorded as a clinical observation in 26 instances; but, as absence of this involvement is very rarely noted, it will be better to take for an estimation of its frequency the number of cases in which it is found at post-mortem examination, namely 23 out of 915, or 2·5 per cent.

**Broad Ligaments.**—Spread from the uterus into the broad ligaments is recorded in 120 cases (13·11 per cent.). But these structures are so often matted to their surroundings by adhesions and peritonitis, and therefore so impracticable of examination that the percentage given is probably considerably below the actual.

**Ovaries.**—The growth had extended to and involved the ovaries in at least 96 cases (10·5 per cent.), but matting of pelvic structures frequently obscures the point.

**Fallopian Tubes.**—The tubes were involved in 18 cases, that is in 1·96 per cent. Here, again, the question is rendered uncertain owing to matting of the pelvic structures.

**Secondary Growths.**—So far it is fairly easy to differentiate between local continuous spread of the disease and “metastases.” But the estimation becomes more complicated when we have to deal with affected structures normally separated from, but in the process of this disease in continuity with, the originally affected organ. In several cases the omentum becomes adherent to the uterus, to the recto-vesical pouch, or to the pelvic contents generally, and the same applies to the intestine, so that there is a continuous dissemination and not what is generally reckoned as true secondary growth. Giving a fairly liberal interpretation to “metastases” it is estimated that 187 or 20·44 per cent. of the cases showed visceral or parietal secondary deposits, and that 351 showed deposits in lymphatic glands (38·36 per cent.): of the former no lymphatic spread is recorded in 55 cases, so that the total number of cases with secondary deposits is 406 (45 per cent. of all post-mortem cases). The following organs were affected:

Liver	.	.	.	122 cases	13·5 per cent.
Lungs	.	.	.	55 „	6·0 „ „
Kidneys	.	.	.	23 „	2·6 „ „
Suprarenals	.	.	.	16 „	1·9 „ „

Heart . . . . .	9 cases	1.0 per cent.
Spleen . . . . .	9 "	1.0 " "
Pancreas . . . . .	8 "	.9 " "
Gall-bladder . . . . .	5 "	.6 " "
Diaphragm . . . . .	6 "	.7 " "
Abdominal wall . . . . .	4 "	.4 " "
Thoracic wall . . . . .	3 "	.3 " "
Subcutaneous . . . . .	3 "	.3 " "
Thyroid gland . . . . .	1 "	.1 " "
Œsophagus . . . . .	1 "	.1 " "
Mamma . . . . .	1 "	.1 " "
Bones . . . . .	8 "	.9 " "
Intestines . . . . .	8 "	.9 " "
Pleurae . . . . .	13 "	1.4 " "
Peritoneum . . . . .	45 "	5.0 " "
Pericardium . . . . .	1 "	.1 " "

With regard to the subcutaneous tissues above, one was a case of general carcinomatosis; in the second case the subcutaneous mass was in the region of the axilla; and in the third case the metastatic nodule was at the ankle. In addition to the 8 cases of intestinal metastases (distributed as follows: pylorus 3, duodenum 2, jejunum 2, and appendix 1), the adherent intestines were affected in 22 cases. The osseous deposits included 1 in the skull, 1 in the ribs, 2 in the vertebral column, 1 in the tibia, and 2, which were probably due to a continuous spread, in the innominate bone; the sacrum was affected once.

Of the 351 cases of deposits in the lymphatic glands, the distribution was as follows:—

Axillary . . . . .	1
Supraclavicular . . . . .	6
Thoracic . . . . .	17
Higher Abdominal . . . . .	31
Lumbar . . . . .	305
Pelvic . . . . .	250
Inguinal . . . . .	45

Under the term "higher abdominal" are included the mesenteric, portal, cœliac, and higher pre-vertebral glands; under the "thoracic" are included the mediastinal and



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bronchial glands. Owing to the matting together of the pelvic structures and the common post-mortem method of removing the pelvic contents *en masse*, a precise description of the involvement of the intra-pelvic glands is practically impossible.

*Matting of the Pelvic Structures.*—This condition is recorded in 221 cases (25 per cent.).

### Other Post-mortem Appearances.

Œdema of the lower extremities, 110 cases (12 per cent.).

*Brain.*—The conditions found were œdema of the brain five times, sub-arachnoid effusion six times, cerebellar abscess once, extra-dural hæmorrhage once, sub-dural hæmorrhage twice, aneurysm of the vertebral artery once, and cerebral hæmorrhage twice.

*Thyroid Gland.*—In 7 cases adenomata of the thyroid were found, in 6 cases thyroid cysts, once (a case of myxœdema) fatty degeneration, and in 63 the gland structure showed colloid degeneration.

*Lungs.*—Pneumonia was present in 93 cases (10 per cent.), bronchitis in 19 (2 per cent.), active tuberculosis in 15 (1·6 per cent.), old or dormant tuberculosis in 174 (19 per cent.), pulmonary infarctions in 11 (1·2 per cent.), and abscesses in 4 (0·4 per cent.).

*Heart.*—Vegetations on valves were found in 84 (9 per cent.), aneurysm of the left ventricle in 1, changes in the heart muscle—such as softening, fatty infiltration, and brown atrophy—in 160 (17·5 per cent.). Patency of the foramen ovale was noted in 38 (4 per cent.).

*Liver.*—Fatty change and cirrhosis were recorded in 385 cases (42 per cent.), hydatid cysts in 7, and a dermoid once; 1 case showed a hepatic infarction, and 1 syphilitic cirrhosis.

*Stomach.*—The condition of hour-glass stomach was observed in 1 case, and gastric ulcer in 8.

*Spleen.*—Splenic abscess was noted in 2 cases, a splenic cyst once, miliary tubercle once, and infarctions in 10 cases.

*Suprarenals.*—Adenoma of the suprarenal was noted once, a cyst once, and great hypertrophy in a third case.

*Gall-bladder.*—Calculi of the gall-bladder were seen in 49 cases (5·4 per cent.).

*Kidneys.*—The kidneys were hydronephrotic and the ureters dilated in 692 cases (75 per cent.). In 76 instances the pelves of the kidneys contained pus. Calculi were found in 6 cases, and infarctions in 7. The kidney substance itself was described as pale, fatty, granular, or fibrotic in 351 cases (38.4 per cent.). Tuberculosis was met with in one instance.

*Peritonitis.*—General peritonitis occurred in 65 cases (7 per cent.).

*Pelvic Abscesses.*—Pelvic abscesses occurred in 47 (5 per cent.); 11 of these had perforated into the vagina.

*Psoas Abscesses.*—Abscesses in the psoas muscle were observed in 5 cases (5 per cent.).

*Bladder.*—Cystitis was present in 55 cases in which no extension of the growth to the wall of this viscus had occurred. Calculi of the bladder occurred twice, and rupture of the bladder took place once.

*Ovaries.*—These were atrophied in 101 cases (11 per cent.), in 4 cases dermoid cysts of the ovary were present, and in 13 the ovary was the seat of an abscess. In 20 cases (2 per cent.) the ovaries were described as cystic, in 16 an ovarian cystoma was present, and in 4 a multilocular cystoma. Fibroma of the ovary was noticed once.

*Fallopian Tubes.*—In 50 cases (4 per cent.) the tubes were distended, in 4 instances with blood, in 24 with pus, and in 22 with serous fluid. In one case a fibroid of the tube was present and in another an adenoma. Broad ligament cysts were found in 6 cases.

*Uterus.*—Fibroids were observed in 54 cases (6 per cent.). Retained products existed in 2.

*Lardaceous Disease.*—Fourteen cases showed this condition, the liver in 11, the spleen in 12, and the kidneys in 5.

Meckel's diverticulum was present in 6 cases.

Atheroma was noticed in 235 cases (26 per cent.).

*Thrombosis.*—The iliac veins were recorded as being thrombosed in 29 (3 per cent.), and the inferior vena cava in 4 cases.

Plugging of the thoracic duct (4 cases), spinal curvature (3), diphtheritic false membrane (2), parotitis, tubercular peritonitis, caries of the sternum, fatty degeneration of the

bony pelvis, and accessory nipple (1 of each), complete the list of pathological conditions met with in the 915 autopsies.

### Histology.

The series of 151 cases which supplied material for histological examination includes 98 carcinomata of the squamous-cell type, 10 of the columnar-cell, 5 of the spheroidal, 5 sarcomata, and 19 endotheliomata; in addition to these, there were 14 cases of uncertain histology.

**Squamous-cell Carcinoma.**—The squamous-cell carcinomata may be subdivided further according to the various epidermal layers present. *All layers* were present in 22 post-mortem cases, 4 of these showed no metastases, 8 glandular only, 5 visceral only, and 5 combined visceral and glandular metastases.

*The Malpighian and Prickle layers* were present in 1 operation case and 20 post-mortem; of the latter, 5 showed no metastases, 5 glandular only, 4 visceral only, and 6 combined glandular and visceral metastases.

*The Prickle and Keratinising layers* were present in 14 post-mortem cases; of these, 5 showed no metastases, 4 glandular only, 2 visceral only, and 3 glandular and visceral.

*The Malpighian layer alone* was present in 13 post-mortem cases; 4 gave no metastases, 3 glandular only, and 6 visceral and glandular.

*The Prickle layer alone* was present in 13 post-mortem cases; 4 gave no metastases, 3 glandular only, and 2 glandular and visceral.

*The Malpighian and Keratinising layers alone* were present in 1 case, with visceral and glandular metastases.

Differentiation between the layers was impossible of accuracy in 2 operation and 12 post-mortem cases; of the latter, 3 gave no metastases, 4 glandular only, 1 visceral only, and 4 glandular and visceral.

**Columnar-cell Carcinoma.**—This type was represented by 1 operation and 9 post-mortem specimens; the latter gave no metastases in 4 cases, glandular only in 1, visceral only in 2, and combined visceral and glandular in 2.

**Spheroidal-cell Carcinoma.**—This sub-division includes 5 cases, 1 of which had no metastases, 1 visceral only, and 3 visceral and glandular.

**Sarcomata.**—The sarcomata were represented by 5 cases, 2 of the spindle-cell variety, 2 of the small mixed-cell and 1 of the large round cell variety; 3 cases had no metastases, the small mixed-cell tumour had associated liver-deposits, and one of the spindle-cell sarcomata had metastases in the omentum, peritoneum, and lymphatic glands.

**Endotheliomata.**—There were 19 examples of this class; 3 showed no metastases, 4 glandular only, 4 visceral only, and 8 visceral and glandular.

**Tumours of Uncertain Histology.**—These comprise cases in which the histological preparation was at fault, or in which exact details of the structure could not definitely be decided upon. One of these was an operation specimen, and 13 were obtained from the post-mortem room. In 7 cases there were no metastases, in 1 glandular only, and in 5 combined glandular and visceral deposits.

## II.—MALIGNANT DISEASE OF THE CORPUS UTERI.

### GENERAL DETAILS.

Sixty-nine cases were the subject of analysis, 11 of these being sarcoma.

**Civil Condition.**—Forty-seven were married and 11 single. Among the married 25 had borne one or more children, 7 had produced only miscarriages, and 7 were barren—that is to say, a quarter were absolutely sterile.

**Family History.**—Twenty-three had a family history free from a cancerous or a phthisical taint (48 per cent.), 16 a phthisical history (33 per cent.), and 11 (23 per cent.), a history of cancer. Of the last there was a homologous heredity in one, the patient's sister being affected with uterine cancer. Two cases had a family history of cancer and phthisis (4·2 per cent.).

**Menstrual History.**—The average age at onset of menstruation was 14·6 years. Nine cases had a periodicity of one month, one of three weeks, one of 6-7 weeks, and one of 5-7 weeks. The average duration of the menstrual flow was



5-6 days. Twenty-five cases were recorded as regular and one as irregular. The quantity of blood lost at each period was scanty in 2 and profuse in 6. The average menopause age of 33 cases was 48 years.

**Age at Onset of Disease.**—The age at onset can be calculated from particulars given in 52 cases, and is 51 years. Taking the sarcomata apart from the rest, the average age of onset in 6 cases is 48·46 years.

*Relation to the Menopause.*—Of the 11 cases of sarcoma, 5 commenced before the menopause, one at the time of, and 5 after; while of the others, 12 were previous to, 2 were at, and 44 were subsequent to, the menopause. Taking the two groups together, cancer of the body occurred after the menopause in 71 per cent., at the menopause in 4 per cent., and before the menopause in 25 per cent.

**Duration.**—The average duration from the beginning of symptoms till death in 30 cases, including one sarcoma where the approximate duration was 6 months, was 1·83 years.

#### CLINICAL DETAILS.

Pain was present in 46 and absent in 1.

Hæmorrhage was given as a symptom in 31 cases and noted as absent in 6. Thirty-one cases had an offensive vaginal discharge, and 3 were free from this sign.

Emaciation is recorded in 34 cases and its absence in 7; of the latter only one evinced emaciation at the time of post-mortem examination. Swelling of the abdomen is recorded in 16. Twelve of the patients had troubles of micturition.

Uterine fixity was observed clinically in 22 cases.

Ascites was present in 8 cases. Fifteen of the patients complained of such gastric disturbances as anorexia, nausea and vomiting.

Peritoneal masses could be felt in 9 cases.

#### Operations.

Nine patients had hysterectomy performed on them; 4 of these left hospital and were lost sight of, 3 died within a day or two of operation, one died 2 years after operation, and 1 returned with an inoperable recurrence in the abdominal wall 5 years after hysterectomy for sarcoma.

Exploratory laparotomy was done in 6 cases, 2 died following operation, 1 was alive two years afterwards, and the rest were lost sight of.

Colotomy was performed in 5 cases for relief of obstruction; 1 of these patients went out after operation, and of the others the longest survival was 2 months. Four cases had previously been curetted or had a mucous polypus removed, 1 died 3 months afterwards, and the rest were lost sight of.

#### PATHOLOGICAL DETAILS.

This section is the analysis of 33 autopsies. None of the cases diagnosed as sarcoma came to post-mortem examination.

In 5 cases the growth was confined purely to the uterine body.

**Glandular Deposits** were found in 15 (45 per cent.) with a distribution as follows: pancreatic 1, mesenteric 2, pelvic 2, iliac 2, lumbar 7, aortic 1, and inguinal 1.

**Metastases in the Viscera.**—Visceral deposits were found in 16 (48.5 per cent.) The liver was affected in 5 cases (15 per cent.); lungs, 5 (15 per cent.); intestines, 4 (12 per cent.); peritoneum, 9 (27 per cent.). The spleen, pericardium, pleura, diaphragm, and ribs, had metastases in one case each.

**Local Spread.**—Extending by continuity the malignant process involved the broad ligaments in 4 cases, the ovaries in 4, the Fallopian tubes in 1, the bladder in 3, and the rectum in 4. The vagina became involved in 3 cases in which it was free at the last recorded clinical examination; in 2 other cases of sarcoma it was found clinically to be affected, in one of which it had spread as far as the vulva. Recto-uterine fistulae were found in 6 cases, and utero-vesical in 1.

**Other Post-mortem Appearances.**—The pelvic structures were matted together in 15 cases (45 per cent.). Hydro-nephrosis occurred in 11 (33 per cent.), peritonitis was found in 3 (10 per cent.) and pelvic abscesses in 4. Atheroma occurred 12 times, fatty degeneration of the heart 4, patent foramen ovale 1, ovarian cyst 1, fibroma of the kidney 1, cystitis 2, rickets 1, fibroids 4 (12 per cent.), old phthisis 2, pneumonia 2, gall-stones 4, hydrosalpinx 3, thrombosis of the iliac vein 1, tubercular peritonitis 1, fatty change in the liver 11 (33 per cent.), and fatty change in the kidneys 4.

### Histology.

The histological material was derived from 11 autopsies and 5 operations. Of the latter 4 were carcinomata of the columnar-cell type, one of which was becoming transitional, and the fifth was a spindle-cell sarcoma. Of the post-mortem specimens, 5 were carcinomata of the columnar-cell type (all but one becoming transitional), and all had associated metastases in the glands and 4 in the viscera, viz. liver and peritoneum, omentum and ovary, spleen and peritoneum, liver and vertebræ; 4 were of the spheroidal-cell type, 3 of them having associated metastases, viz. intestine and glands, glands alone, and peritoneum and omentum; 1 was a hæmorrhagic round-cell sarcoma with associated glandular deposits; and one was a lymphatic perienthelioma with metastases in the pancreas, duodenum, kidney, adrenal, vertebræ, and glands.

## III.—MALIGNANT DISEASE OF THE VAGINA.

### GENERAL DETAILS.

Fifty-seven cases are here dealt with.

**Civil Condition.**—Forty-four (88 per cent.) were married and 6 (12 per cent.) were single. Of the married 27 had borne children and 5 were barren.

**Family History.**—Twenty-two cases gave a history free from cancer or phthisis (58 per cent.), 11 (29 per cent.) had a phthisical history, and 8 (21 per cent.) a family history of cancer, 3 cases (8 per cent.) had a mixed history of cancer and phthisis.

**Age at Onset.**—From particulars supplied regarding the appearance of symptoms, the average age at onset has been calculated from 40 cases and is 46·42 years. The youngest patient was 22 and the oldest 64·5. Of the total number of cases dealt with, 22 (38·6 per cent.) occurred before, 32 (56 per cent.) after, and 3 (5·3 per cent.) at the time of the menopause.

**Duration.**—The average duration calculated from 25 cases is 1·25 years. The longest duration was 3½ years, and the shortest 6 months.

## CLINICAL DETAILS.

Local pain was present in 38 and absent in 1. Hæmorrhage occurred in 18 and did not appear in 4 cases. Offensive discharge was noted in 32 cases. Troubles of micturition were complained of in 22 cases, and pain or difficulty in defæcation in 4. Emaciation was observed in 32 and absent in 3. Vomiting was complained of in 2.

## PATHOLOGICAL DETAILS.

Twenty-two cases were the subject of post-mortem examination.

**Site of Growth.**—In 10 instances the anterior wall was affected, in 9 the posterior wall, in 1 the right side, and 1 the left.

**Local Spread.**—The growth extended upwards to the cervix in 8 cases, downwards into the vulva in 13, anteriorly into the bladder in 14, and posteriorly into the rectum in 7. "Contact" ulcers were noted in 2 cases. Among the post-mortem cases, fistulous communications existed with the bladder in 7 and with the rectum in 5.

Among the clinical cases, where no post-mortem examination was carried out, 3 had vesico-vaginal fistulæ, 2 recto-vaginal, and 1 a double fistula.

**Metastases.**—Glandular deposits were observed in 8 cases (36 per cent.), the distribution being as follows: Inguinal 4, pelvic 1, iliac 3, mediastinal 1, and bronchial 2. Visceral deposits occurred in 6 cases, distributed as follows: Liver 5, lungs 4, kidneys 3, and ovaries 2.

**Other Post-mortem Appearances.**—Hydronephrosis occurred in 6 cases, fatty liver in 12, fatty heart in 3, atheroma in 6, fibro-fatty kidneys in 8, old pulmonary tubercle in 4, atrophy of the ovaries in 3, uterine fibroids in 6, and bronchitis, broncho-pneumonia, endocarditis, cystitis, adenoma of the thyroid, renal calculus, gall-stones and lardaceous degeneration of liver, spleen, and kidneys, in 1 each.

## Histology.

The 6 cases histologically examined were squamous carcinoma. Four of these showed cell-nests, 2 of them being composed of cells principally of the prickly type, and these



were the only two cases of the 5 post mortems to give visceral or glandular metastases, the liver being affected in both instances.

#### IV.—MALIGNANT DISEASE OF THE VULVA.

##### GENERAL DETAILS.

The following statistics were compiled from a total of 98 cases.

**Civil Condition.**—Cancer of the vulva occurred in 73 married women and 13 unmarried, or  $6\frac{1}{2}$  times as often in the former as in the latter. Forty-nine women were stated to have borne children and 27 were barren.

**Family History.**—Of 65 cases in which the family history is recorded, 12 (18·5 per cent.) gave a history of cancer; 22 (33·8 per cent.) gave a history of phthisis (5 giving a history of both phthisis and cancer); and 36 or 55·4 per cent. came of a more or less healthy stock.

**Age at Onset.**—The approximate age at onset, reckoned from the first appearance of a local lesion, has a wide range, the earliest being 25 and the latest 78. The mean age at onset of the disease is 51·82 years. This estimation, which is based on 77 cases, is considerably lower than that of Mr. Ball in the present volume of the Archives. His 16 cases extending over the last ten years include only one below the age of 42, whereas of the 77 cases here considered 15 were below that age. A careful scrutiny of these 15 fails to give reasonable grounds for their rejection.

In this estimation only those cases are reckoned in which the approximate time of onset was given, but the less restricted latitude of the division into quinquennial age-periods allows of use being made of 97 cases in all, which may be grouped as follows:—

25	30	35	40	45	50	55	60	65	70	75
to	to	to	to	to	to	to	to	to	to	to
29.	34.	39.	44.	49.	54.	59.	64.	69.	74.	79.
8	5	6	9	18	9	14	10	8	6	4

From cases in which precise particulars are given or certainly deducible regarding the cessation or continuance of the menstrual flow it may be concluded that 30 per cent. (24

cases) occur before, 12.5 per cent. (10 cases) occur at, and 57.5 per cent. (46 cases) occur after the menopause.

**Duration.**—The longest recorded span after the onset of cancer of the vulva was 7 years and the shortest 6 months; but in the former case the patient had been operated upon two years after the onset. In untreated cases the greatest duration was 5½ years. The average duration of all cases, treated and untreated, was 2.4 years. The 26 cases unoperated upon give an average duration of 2 years. The onset age does not appear to have much influence on the duration of the disease as the following table shows:—

Age {	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.	50 to 54.	55 to 59.	60 to 64.	65 to 69.	70 to 74.	75 to 79.
Duration of disease in individ- ual cases.	1.25	1.5	1.25	5.5	5.5	1.0	5.0	1.25	0.5	—	1.5
	—	—	—	2.0	0.75	2.0	1.75	0.75	2.0	—	1.25
	—	—	—	3.0	2.25	3.0	1.25	3.0	1.0	—	—
	—	—	—	1.5	5.0	—	—	—	1.25	—	—
	—	—	—	—	—	—	—	—	1.0	—	—
Average -	1.25	1.5	1.25	3.0	3.4	2.0	2.7	1.0	1.15	—	1.4

#### CLINICAL DETAILS.

Of 76 cases in which the first symptoms have been noted there was a previous history of pruritus vulvæ in 8 (10.5 per cent.), of local injuries such as blows or scratches in 4, of "feelings of local irritation" in 4, of abscesses in 1, and of vulvar lupus in 1. In addition to these, 2 cases are recorded in which tumours had preceded the definite malignant lesion, the one (untreated) by 9 years, the other removed by cauterization 25 years before the occurrence of any noticeable re-formation in situ. The former may have been a malignant tumour of slow evolution or a simple tumour assuming malignant characters, while the latter may have been a rare instance of late recurrence, but they have been treated as doubtful cases and are omitted from the paragraph dealing with "durations."

**Local Appearances.**—The lesion attracts the notice of the patient first of all as a small nodule, wart, or ulcer, which may be painless at the beginning. According to the histories given by the patients the unabraded nodule seems to be five

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times as common as the small ulcer. Local pain is recorded in 49 cases, in 29 of which it existed before a definite lesion was discovered or was the means of directing the patient's attention to it; in 13 cases the onset of pain was of subsequent occurrence; and in 4 cases pain was not in evidence during the course of the disease.

### PATHOLOGICAL DETAILS.

**Site.**—In many cases owing to the advanced state of the disease when the patients presented themselves, it is impossible to determine what part of the vulva was primarily attacked, while some of the cases herein reckoned may have been primary in the lower part of the vagina with vulvar extension; but any error that there may be is a small one. The right side was affected primarily or mostly in 29 instances, the left side in 28, the clitoris in 7, the vestibula or meatus urinarius in 7, the posterior part in 5, and both sides equally in 12. Ulceration of the opposite side ("contact ulcer") was observed on 4 occasions.

**Local Extension.**—In 85 cases in which the local spread is recorded the opposite side or both sides became affected 21 times (24·7 per cent.), longitudinal extension occurred 14 times (16·5 per cent.), the clitoris became affected 7 times (8·2 per cent.), the urethra or its meatus 9 times (10·6 per cent.), the vagina 36 times (42·4 per cent.), the inguinal glands, on the same side 35, on both sides 25, and on the opposite side on one occasion. The anus or rectum was involved 7 times and the bladder once by direct extension. The inguinal glands were unaffected in 6 cases.

In the case in which the inguinal glands on the opposite side were involved the spread had probably taken place through the clitoris, which was affected by extension.

**Secondary Growths.**—33 post-mortem records are made use of, in 16 of which no secondary deposits were discovered.

Glandular metastases were observed in 13 cases (39·4 per cent.) with a distribution as follows:—

Iliac glands . . . . .	3
Pelvic glands . . . . .	7
Lumbar glands . . . . .	6
Supraclavicular glands . . . . .	1

Visceral deposits were discovered in 6 cases (18·2 per cent.) viz.: liver 3; lungs 2; heart 2; spleen, kidney, urinary bladder, uterus, rectum, pleura, peritoneum, pelvic floor, diaphragm, pectoral muscle, 1 case each.

A case of melanotic sarcoma of the right labium minus (not included in the above), in which the tumour had been removed without local recurrence, showed at the autopsy glandular metastases in the right inguinal, iliac, retroperitoneal, and bronchial lymphatic glands, and visceral deposits in the right frontal lobe of the brain, in the pia mater and ependyma of the lateral ventricles, in the heart, lungs, parietal pleuræ, peritoneum, stomach, liver, kidneys, ovaries, small intestines and colon, together with a rupture into and a thrombosis of the hepatic vein.

#### Other Post-mortem Appearances.

*Lungs*.—Twelve cases showed more or less œdema or emphysema of the various lobes. In 5 instances (15·2 per cent.) evidences of past or present tuberculosis were observed.

*Heart*.—Nine cases showed vegetations on, or atheroma of, the valves. In 2 instances the heart was fatty.

*Liver*.—In 17 cases (51·5 per cent.), the liver exhibited fatty change, in one case syphilitic cirrhosis was present, and in one instance hydatid cysts were found.

*Spleen*.—In 4 cases the spleen was very soft and almost diffuent. In one case an abscess was found.

*Kidneys*.—In 12 cases the kidneys were pale, in 5 granular and contracted, in 2 hydronephrotic, in 2 there were multiple cysts in the cortex, in 2 pyelitis was present on one side, in 2 cases the organs were congested, and in one instance there were infarcts. Dilatation of the ureter was found once.

*Uterus*.—In 11 cases fibroids were found in the uterus (33·3 per cent.).

*Ovaries*.—In 6 cases the ovaries were atrophied.

*Thyroid Gland*.—In one instance an adenoma was found, and in two, colloid degeneration.

*Emaciation*.—The post-mortem records give the definite absence of emaciation in 7 instances (21·2 per cent.). In only one of these cases was there any metastatic deposit in the



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viscera. The clinical notes mention the presence of emaciation in 20 cases and its absence in 13.

*Edema and Thrombosis.*—The lower extremities were cedematous in 7 cases (21·2 per cent.). In one case there was thrombosis of the femoral and common iliac veins, and in another the external iliac artery was affected.

### Histology.

Twelve cases were histologically examined, two being operation specimens and the others obtained at autopsy. Of these, 11 were squamous carcinomata and one was a rodent cancer removed at operation. All the epidermal layers entered into the formation of the growths in 4 cases, in 2 the Malpighian and keratinizing layers, in one the prickle and keratinizing layers, and in one the prickle layer alone; in 3 no differentiation was made between the layers. Of the 10 autopsies, in two cases only were there visceral metastases—in one case the peritoneum, pleura, and lungs, and in the other the lungs; in 6 there were glandular metastases, in two of which the inguinal glands alone were affected. In two cases no metastases at all were found.

In the following table some of the figures given in the preceding pages are collated for convenience of reference.

	Cervix.	Body.	Vagina.	Vulva.
	Per cent.	Per cent.	Per cent.	Per cent.
Married women ... ..	95	68·1	88	84·9
Parous ... ..	79·6	59·6	61·4	67·1
Phthisical family history ...	37·1	35·3	29	33·8
Cancerous " " ...	16·1	23	21	18·5
Phthisis and cancer history	5·9	4·2	8	7·7
	Years.	Years.	Years.	Years.
Mean age at onset ... ..	44·6	51	48·4	51·8
	Per cent.	Per cent.	Per cent.	Per cent.
Onset before menopause ...	51	25	38·6	30
" at " " " ...	9	4	5·3	12·5
" after " " " ...	40	71	56	57·5
	Years.	Years.	Years.	Years.
Mean duration ... ..	1·74	1·83	1·25	2·4
	Per cent.	Per cent.	Per cent.	Per cent.
Pain present ... ..	95	98	97·4	92·5
Hæmorrhage ... ..	95	83·8	81·8	—
Emaciation ... ..	81·6	82·9	91·5	60
Fistulæ (autopsies) ... ..	72	21·2	55·5	—
Visceral metastases ... ..	20·5	48·5	24	18·2
Glandular metastases ... ..	38·4	45	36	39·4
Uterine fibroids ... ..	6	12	27·6	33·3

# ON THE ELECTRICAL AND PHOTOGRAPHIC PHENOMENA MANIFESTED BY CERTAIN SUBSTANCES THAT ARE COMMONLY SUPPOSED TO BE ÆTIOLOGICALLY ASSOCIATED WITH CARCINOMA.

By W. S. LAZARUS-BARLOW, M.D., F.R.C.P.

## I.—INTRODUCTION.

SINCE the adoption of X-rays as a method of treatment for various diseases, and the consequent installation of powerful electric apparatus at hospitals, several cases of a pathological condition which is, histologically, a true squamous cell carcinoma of the hand, have occurred amongst the electrical medical officers and the makers of the electrical apparatus for the production of X-rays. Three cases of this kind, all of which necessitated amputation of the affected part, and one of which has been followed by the formation of metastatic deposits and subsequent death of the patient, have come under the author's personal observation.

Further, it has long been held by the medical profession, though without actual proof, that certain substances play an important part in causing certain varieties of cancer. Thus the smoking of clay pipes, particularly if the mouthpiece be not protected with sealing-wax or other similar substance, has held to be largely accountable for the common occurrence of cancer of the lip in men, and its great rarity in women. In the same way soot has been associated with "chimney-sweeps' cancer" of the scrotum; paraffin and tar have been associated with the cancer of the skin of the arms of persons employed in the manufacture of these substances; arsenic with the cancer that is met with amongst workers in arsenic; betel nut with cancer of the tongue, especially in Ceylon; and

gallstones with cancer generally, but particularly with cancer of the gall-bladder.

Of all these associations of a physical agent with the occurrence of cancer, the most striking is that concerning the workers with X-rays. It is further noteworthy that all those examples of cancer which are commonly associated with a definite physical agent, such as those which have been mentioned above (with the exception of cancer of the gall-bladder), are concerned with the one histological type of squamous cell carcinoma. This is in marked contrast with other varieties of "cancer," including the sarcomata, in which any physical agent which may be inculpated is of a highly indefinite kind, e.g. a blow or fall.

Since, therefore, a group of cancerous disease, i.e. squamous cell carcinoma, has been more or less commonly associated with a group of physical agents, it was desirable to ascertain, if possible, whether they contained one common factor; and since the association between the emanations from Crookes' tubes and carcinoma of the hand seems indubitable, it was decided to investigate whether the other substances that have been mentioned manifest evidences of radio-activity.

## II.—METHODS.

**Electrical Methods.**—The electrical investigations were carried out by determining either (1) the length of time required for the charged leaves of an electroscope to travel towards one another over a measured distance, or (2) the distance that the charged leaves travelled towards one another in a definite time. The results given below are those obtained by one or other or both of the above methods under varying conditions.

*The Electroscopes.*—Metal gold-leaf electroscopes were used in all cases. The gold-leaves were fastened to a piece of fine platinum-iridium wire bent at a right angle, and flattened from side to side. This wire was fixed at its upper end into a vulcanite rod (1 in. in length and  $\frac{1}{2}$  in. in diameter) that passed through the top of the electroscope. A similar vulcanite rod, drilled throughout its length, also passed through the top of the electroscope at a distance of half an inch from the vulcanite rod carrying the wire with the gold

leaves, and carried a Z-shaped piece of platinum-iridium wire which moved freely, and was designed for charging the leaves. The apparatus was arranged so that the gold leaves hung in the centre of the electroscope antero-posteriorly, and from right to left, but slightly more in the upper half of the electroscope. In one case the body of the electroscope was of tinned iron, but in the other six the metal was lead; these instruments were cylinders, with a transverse and vertical measurement of 4 in., and the lead walls were  $\frac{1}{8}$  in. in thickness. A circular hole for observation of the leaves,  $\frac{1}{2}$  in. in diameter, was drilled in the body of the instruments, and the leaves were arranged so that they presented sharp edges to the eye. The electroscopes rested evenly upon a thick lead base that was completely earthed, but were not fixed to the base to allow of the introduction of the various substances to be investigated. The top of the electroscope was securely fixed on by white lead. One of the lead electroscopes and the tinned iron electroscope were reserved for tentative work, and all conclusions derived from their use were tested on the other lead electroscopes, which were kept within a glass-fronted cupboard in a separate room of approximately constant temperature. The air in the cupboard was kept dry by means of six large dishes of quicklime. The cupboard was provided with electric lamps, so disposed that light from them thrown on concave mirrors placed in front of the openings in the electroscopes within the cupboard illuminated the interiors of the instruments. By this arrangement of electroscopes, mirrors, and lamps, it was possible to take readings whenever necessary without opening the cupboard; in fact, except for the necessary lighting of the lamps when an observation was to be made (and this was done by means of a plug for each lamp outside the cupboard), the experiments were entirely undisturbed throughout their whole course. In a large proportion of the cases initial and terminal observations alone were made.

The length of time required for complete discharge of the electroscopes from a given point of separation of the leaves differed in different electroscopes. In the case of those placed within the cupboard periods varying from fifty-two to sixty-three hours were necessary for the



complete discharge of the amount of electricity sufficient to separate the leaves for a distance represented by 14 mm. on a scale attached to the electroscope across the lower part of the opening in front. The other lead instrument, which was kept under a bell jar, completely discharged in about thirty-three hours, while the leaves in the tinned iron electroscope approximated over a fixed  $\frac{1}{4}$  in. in varying periods, according to climatic conditions, but roughly in twenty minutes. This electroscope was much exposed, and was purposely intended to discharge rapidly.

Care was taken that the observations of the leaves should always be from one spot; and in the case of the instruments within the cupboard and under the bell jar the openings in the mirrors were of such a size that with the forehead against the glass there was only one position at which the two leaves could be seen clearly at the same time. The vertical level for observing the leaves was fixed permanently in each instrument by taking the reading at the level at which the edge of the fixed millimetre scale in front coincided with a fixed horizontal line at the back of the electroscope on its inner surface.

The gold leaves were charged by way of the Z-shaped platinum-iridium wire, the limb of which within the electroscope was sufficiently long to touch the wire carrying the gold leaves. After charging the leaves the charging wire was turned away from the leaves-bearing wire and was discharged. Great care was taken to charge exactly to a constant degree in each instrument, viz. to 14 mm. of distance on the scale between the leaves. It was only when all instruments showed an exact charging after the shutters of the cupboard had been definitely closed that the experiment was commenced.

Readings were taken with great care, and the margin of error in this direction is small; the total margin of error certainly does not amount altogether to more than  $\frac{1}{4}$  mm. in respect of the readings themselves.

**Photographic Methods.**—The substances were exposed to photographic films under various conditions (*a*), for periods of thirty-six days and six and a half months at a temperature of about 18° C; (*b*) for eighteen hours at 53° C; (*c*), for eleven days at -3° C. The substances have been allowed to

act on the film (1) directly; (2) through a glass plate or through a glass film .015 mm. in thickness, or enclosed hermetically within a glass capsule; (3) through a variety of thicknesses of a celloidin film; (4) through thin gutta percha. "Imperial special rapid" plates were used; all the processes of placing the substances on the films and of developing the films were carried out entirely in the dark without the use of a red lamp, and the plates and substances were wrapped in layers of filter paper, filter paper impregnated with paraffin wax, black needle paper, and tinfoil in that order.

**The Substances Investigated.**—These have been as follows:—Three samples of clay pipe, each sample consisting of portions of three distinct pipes from different sources, powdered and mixed; two samples of soot from different localities; one mixed sample of cholesterin gallstones; one sample of impure cholesterin gallstone from a case of columnar cell carcinoma of the gall-bladder; one pure cholesterin gallstone; pure pigment gallstones; four samples of pitch from different localities; two samples of paraffin wax of different origins; one sample each of metallic arsenic, arsenious oxide, coal, and three samples of betel nut. All of these were investigated on many occasions both electrically and photographically.

In addition to the above, uranium nitrate, thoria (Welsbach incandescent gas mantle) pitchblende and radium have been investigated in order to explain, if possible, certain unexpected electrical phenomena. The manner in which the experiment with these substances were conducted will be given under the appropriate headings.

### III.—RESULTS OF EXPERIMENTS.

#### A.—Clay Pipes.

In the following experiments the figures represent the number of millimetres which the charged gold leaves approximated during a period of 48 hours, (1) when the substance was not placed within the electroscope, i.e. control experiment; (2) with the substance present; (3) the substance present within the electroscope but covered with an aluminium top or placed within an aluminium box; (4) certain other conditions.

*Leaves charged —; substance on watchglass and uncovered.*

Control experiment.	Experiment 1.	Experiment 2.
8 $\frac{3}{4}$ mm.	10 $\frac{1}{2}$ mm.	11 $\frac{1}{2}$ mm.
	Experiment 3.	
	10 $\frac{3}{4}$ mm.	

*Leaves charged +; substance on watchglass and uncovered.*

Control experiment.	Experiment 4.	Experiment 5.
8 $\frac{3}{4}$ mm.	10 $\frac{1}{2}$ mm.	10 $\frac{1}{2}$ mm.

*Leaves charged +; substance contained within aluminium box.*

Control experiment.	Experiment 6.	Experiment 7.
9 mm.	10 mm.	9 $\frac{1}{2}$ mm.
	Experiment 8.	
	9 $\frac{1}{2}$ mm.	

*Leaves charged +; substance on aluminium tray and uncovered.*

Control experiment.	Experiment 9.	Experiment 10.
10 mm.	11 $\frac{1}{2}$ mm.	11 $\frac{1}{2}$ mm.

*Leaves charged +; substance on two thicknesses of aluminium and uncovered.*

Control experiment.	Experiment 11.
9 mm.	10 $\frac{3}{4}$ mm.

*Leaves charged +; substance placed direct on lead base of electroscope.*

Uncovered

Control experiment.	Experiment 12.
11 $\frac{1}{2}$ mm.	12 $\frac{1}{2}$ mm.

Covered with aluminium top

Control experiment.	Experiment 13.
10 $\frac{1}{2}$ mm.	11 mm.

*Leaves charged + ; substance placed on a disc of pitch.*

Uncovered

Control experiment.	Experiment 14.
11 $\frac{1}{4}$ mm.	12 $\frac{1}{2}$ mm.

Covered with aluminium top.

Control experiment.	Experiment 15.
10 $\frac{1}{4}$ mm.	11 mm.

From the foregoing experiments it appears that the various samples of clay pipe possessed the power of accelerating the discharge of an electroscope, whether the electroscope was charged with positive or negative electricity; whether the substance was placed direct upon a metallic base or was separated therefrom by a dielectric; and whether the substance was covered by an aluminium cap or enclosed within an aluminium box or not. Experiments 1-11 were conducted with the first mixed sample of clay pipes, experiments 12-13 with the second, and experiments 14-15 with the third.

*Effect on Photographic Plates.* The samples of clay pipe were allowed to act on photographic plates, (1) in the unbroken condition and (2) as a powder. The reason for this difference is that the surface of the pipe is frequently glazed, and under any circumstances is far smoother than the fractured surface. The unbroken pipe was allowed to act directly on the photographic plate for 6 $\frac{1}{2}$  months (two samples), and 36 days (three samples); two powdered mixed samples were allowed to act on the film for 36 days. All of these experiments were carried out at about 18° C. No reduction of silver took place in any instance.

## B.—Gallstones.

The following varieties of gallstone have been examined electrically. One mixed sample of powdered cholesterin gallstones, one powdered specimen of an impure cholesterin gallstone from a case of carcinoma of the gallbladder (defined by the name of the patient "Simmons"), one specimen of a pure cholesterin gallstone from a case of carcinoma of the urinary bladder, and one specimen of pure pigment gallstone.



## 1. Mixed sample of powdered cholesterin gallstones.

*Leaves charged — ; substance on watchglass and uncovered.*

Control experiment.	Experiment 16.	Experiment 17.
9½ mm.	8½ mm.	9½ mm.
	Experiment 18.	
	9 mm.	

*Leaves charged + ; substance on watchglass and uncovered.*

Control experiment.	Experiment 19.	Experiment 20.
9 mm.	9 mm.	8 mm.

*Leaves charged + ; substance contained within aluminium box.*

Control experiment.	Experiment 21.	Experiment 22.
9¼ mm.	9 mm.	8½ mm.
	Experiment 23.	
	8¾ mm.	

*Leaves charged + ; substance on aluminium tray and uncovered.*

Control experiment.	Experiment 24.	Experiment 25.
10¼ mm.	9½ mm.	9 mm.

*Leaves charged + ; substance on two thicknesses of aluminium and uncovered.*

Control experiment.	Experiment 26.
9 mm.	8¼ mm.

*Leaves charged + ; substance placed on paraffin disc.*

Uncovered

Control experiment.	Experiment 27.
9½ mm.	9 mm.

Covered with aluminium cap

Control experiment.	Experiment 28.
8½ mm.	8½ mm.

2. Gallstone (Simmons).

*Leaves charged + ; substance placed on paraffin disc.*

Uncovered	
Control experiment.	Experiment 29.
9½ mm.	8¼ mm.
Covered with aluminium cap.	
Control experiment.	Experiment 30.
8½ mm.	8 mm.

3. Pure cholesterin gallstone.

*Leaves charged + ; substance placed direct on lead base of electroscope.*

Uncovered	
Control experiment.	Experiment 31.
10¼ mm.	9½ mm.
Covered with aluminium cap.	
Control experiment.	Experiment 32.
8½ mm.	8¼ mm.

*Leaves charged + ; substance placed on top of aluminium box.*

Uncovered	
Control experiment.	Experiment 33.
9 mm.	7¾ mm.
Covered with aluminium cap.	
Control experiment.	Experiment 34.
6¼ mm.	6 mm.

4. Pure pigment gallstones.

*Leaves charged + ; substance placed direct on lead base of electroscope.*

Uncovered	
Control experiment.	Experiment 35.
11½ mm.	12 mm.
Covered with aluminium cap.	
Covered experiment.	Experiment 36.
10½ mm.	10¼ mm.

From the foregoing experiments it appears that the cholesterolin gallstones (whether relatively pure or impure) tended to retard the discharge of an electroscope whether they were placed on a metal base or on a dielectric and whether they were covered with an aluminium cap or enclosed in an aluminium box or not. Although the bulk of the experiments support these conclusions, experiment 35 indicates that the pigment gallstones did not exert a retarding, but an accelerating influence on the discharge of an electroscope.

*Effect on Photographic Plates. Prolonged exposure at 18° C.*—Six gallstones, two of which were the pure cholesterolin and the pure pigment stones used in the preceding electric experiments, and the powdered impure cholesterolin gallstone (Simmons) were allowed to act upon photographic plates. The pure cholesterolin and the pure pigment gallstone gave marked evidence of reduction of silver, and one impure cholesterolin gallstone gave slight but definite evidence of action (*see Plate*). In all cases the particular substance was allowed to act directly upon the film, and with the exception of the gallstone (Simmons), in which the contact was for 36 days, the substances were allowed to act for 6½ months. In all instances the reduction of the silver took place only in that film with which the gallstone was in close relation, and in no instance did reduction take place where the gallstone was separated from the film by a layer of glass.

*Exposure for 18 hours at 53° C.*—The pure cholesterolin gallstone, gallstone "Simmons," and a number of pigment gallstones were examined photographically in this way: (1) in direct contact with the film; (2) separated from the film by thin glass, by tin foil, or by a film of celloidin; (3) at a short distance from the photographic film but without any intervening substance. The pure cholesterolin gallstone gave evidence of a profound action on the photographic plate when in direct contact, and when at a short distance from the plate without intervening substance, and when separated from the plate by a thin film of celloidin recently prepared (*see Plate*); through thicker celloidin, through thin glass, and through tin-foil, the gallstone did not produce any reduction of silver in the photographic plate. Under similar conditions to those given for the pure cholesterolin gallstone, the gallstone "Sim-

mons" and all the specimens of pigment gallstone investigated gave absolutely no evidence of an actinic effect.

*Exposure for 11 days at  $-3^{\circ}$  C.*—The pure cholesterin and pigment gallstones were exposed to plates (1) in direct contact with the plate; (2) separated from the plate by thin celloidin or by gutta percha; (3) at a short distance from the plate without any intervening substance. The pure cholesterin gallstone gave slight but definite evidence of actinic action when in direct contact with the film, but not under the other conditions. The pigment gallstones were entirely without actinic effect.

### C.—Paraffin Wax.

*Leaves charged — ; substance on watchglass and uncovered.*

Control experiment.	Experiment 37.	Experiment 38.
11 $\frac{1}{2}$ mm.	10 mm.	10 $\frac{1}{2}$ mm.
	Experiment 39.	
	11 mm.	

*Leaves charged + ; substance on watchglass and uncovered.*

Control experiment.	Experiment 40.	Experiment 41.
10 $\frac{3}{4}$ mm.	11 $\frac{3}{4}$ mm.	11 $\frac{1}{4}$ mm.

*Leaves charged + ; substance contained within aluminium box.*

Control experiment.	Experiment 42.	Experiment 43.
10 $\frac{3}{4}$ mm.	11 mm.	10 $\frac{1}{2}$ mm.
	Experiment 44.	
	10 $\frac{1}{2}$ mm.	

*Leaves charged + ; substance on aluminium tray and uncovered.*

Control experiment.	Experiment 45.	Experiment 46.
11 $\frac{3}{4}$ mm.	10 $\frac{1}{2}$ mm.	10 $\frac{3}{4}$ mm.

*Leaves charged + ; substance on two thicknesses of aluminium and uncovered.*

Control experiment.	Experiment 47.
10 $\frac{3}{4}$ mm.	10 mm.



*Leaves charged + ; substance placed on pitch disc.*

Uncovered.	
Control experiment.	Experiment 48.
11 $\frac{1}{4}$ mm.	10 mm.
Covered with aluminium cap.	
Control experiment.	Experiment 49.
10 $\frac{1}{4}$ mm.	9 $\frac{3}{4}$ mm.

*Leaves charged + ; substance placed direct on lead base of electroscope.*

Uncovered.	
Control experiments.	Experiment 50.
(a) 10 $\frac{3}{4}$ mm.	(a') 9 $\frac{1}{2}$ mm.
(b) 11 $\frac{1}{4}$ mm.	(b') 9 $\frac{3}{4}$ mm.
Covered with aluminium cap.	
Control experiments.	Experiment 51.
(A) 9 $\frac{1}{2}$ mm.	(A') 8 $\frac{1}{2}$ mm.
(B) 10 mm.	(B') 8 $\frac{1}{4}$ mm.

Experiments 37-47 were carried out with one sample of paraffin, experiments 48-51 with a different sample from another source.

From the foregoing experiments it appears that the samples of paraffin wax had the property of retarding the discharge of a charged electroscope under certain conditions. In experiments 40 and 41 this retarding property was apparently changed into an accelerating property when the sole change in the experiment was an alteration of the sign of the electricity with which the leaves are charged : these two experiments, and experiments 55 and 70 were, however, the only examples among 35 experiments in which a reversal from retardation to acceleration occurred with a reversal of the sign of the charge on the gold leaves.

*Effect on Photographic Plates.*—In spite of a lengthened exposure to paraffin wax the silver salt of a photographic plate undergoes no visible change. The paraffin, however, obstructs the influence of actinic rays proceeding from a non-luminous substance in the neighbourhood.

**D.—Pitch.**

Four samples of pitch from different localities were examined electrically, and as regards their effect upon photographic plates.

*Leaves charged — : substance on watchglass and uncovered.*

Control experiment.	Experiment 52.	Experiment 53.
10 mm.	$8\frac{1}{2}$	9 mm.
	Experiment 54.	
	9 mm.	

*Leaves charged + : substance on watchglass and uncovered.*

Control experiment.	Experiment 55.	Experiment 56.
9 mm.	$9\frac{1}{4}$ mm.	$8\frac{1}{2}$ mm.

*Leaves charged + : substance contained within aluminium box.*

Control experiment.	Experiment 57.	Experiment 58.
$8\frac{3}{4}$ mm.	9 mm.	$8\frac{1}{2}$ mm.
	Experiment 59.	
	$8\frac{1}{2}$ mm.	

*Leaves charged + : substance on aluminium tray and uncovered.*

Control experiment.	Experiment 60.	Experiment 61.
10 mm.	10 mm.	10—mm.

*Leaves charged + : substance on two thicknesses of aluminium and uncovered.*

Control experiment.	Experiment 62.
9 mm.	$9\frac{1}{4}$ mm.

*Leaves charged + : substance placed on paraffin disc.*

Uncovered.

Control experiments.	Experiment 63.
(a) $9\frac{3}{4}$ mm.	(a') $9\frac{1}{2}$ mm.
(b) $8\frac{3}{4}$ mm.	(b') $8\frac{3}{4}$ mm.
(c) $6\frac{3}{4}$ mm.	(c') $6\frac{3}{4}$ mm.

Covered with aluminium cap.

Control experiments.	Experiment 64.
(A) $8\frac{1}{4}$ mm.	(A') $8\frac{1}{2}$ mm.
(B) $8\frac{1}{2}$ mm.	(B') $8\frac{1}{4}$ mm.

*Leaves charged + ; substance placed direct on lead base  
of electroscope.*

Uncovered.

Control experiment.	Experiment 65.
$11\frac{1}{2}$ mm.	$11\frac{1}{4}$ mm.

Covered with aluminium cap.

Control experiment.	Experiment 66.
$10\frac{3}{4}$ mm.	$10\frac{1}{4}$ mm.

From these experiments it may be concluded that the samples of pitch examined in Experiments 57-66 were without effect upon the discharge of the electroscope, or that they had a very slight retarding effect. Experiments 52-6 were made with a different sample of pitch to the others, and gave evidence of a definite retarding effect.

*Effects on Photographic Plates.*—Exposed to the photographic film for thirty-six days at  $18^{\circ}$  C, none of the samples of pitch yielded evidence of actinic properties.

### E.—Soot.

Two samples of soot were examined electrically. One contained a considerable admixture of mortar from the chimney, the other was apparently pure.

*Leaves charged - ; substance on watchglass and  
uncovered.*

Control experiment.	Experiment 67.	Experiment 68.
$11\frac{1}{2}$ mm.	$12\frac{1}{4}$ mm.	$11\frac{1}{2}$ mm.
	Experiment 69.	
	$11\frac{1}{2}$ mm.	

*Leaves charged + ; substance on watchglass and  
uncovered.*

Control experiment.	Experiment 70.	Experiment 71.
$11\frac{1}{4}$ mm.	$11\frac{3}{4}$ mm.	11 mm.

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*Leaves charged + ; substance enclosed in aluminium box.*

Control experiment.	Experiment 72.	Experiment 73.
11 mm.	11 $\frac{3}{4}$ mm.	10 $\frac{1}{2}$ mm.
	Experiment 74.	
	10 $\frac{3}{4}$ mm.	

*Leaves charged + ; substance on aluminium tray and uncovered.*

Control experiment.	Experiment 75.	Experiment 76.
12 mm.	12 $\frac{1}{4}$ mm.	10 $\frac{1}{2}$ mm.

*Leaves charged + ; substance on two thicknesses of aluminium and uncovered.*

Control experiment.	Experiment 77.
11 mm.	12 mm.

*Leaves charged + ; substance placed on paraffin disc.*

Uncovered.	
Control experiment.	Experiment 78.
9 $\frac{3}{4}$ mm.	9 $\frac{1}{4}$ mm.
Covered with aluminium cap.	
Control experiment.	Experiment 79.
8 $\frac{1}{4}$ mm.	8 mm.

The results of the experiments are conflicting, except in the case of the last two experiments, which were made with the pure sample of soot. Here the substance produced a retarding effect both when uncovered and when covered with an aluminium cap. The irregularities of Experiments 67-77 probably depend upon the fact that the surfaces presented to the gold leaves consisted of different proportions of mortar and of soot in different experiments.

*Effects on Photographic Plates.*—Exposed for thirty-six days to the photographic film at about 18° C, the pure sample of soot yielded evidence of actinic action; the sample mixed with mortar was without effect. Similar results obtained when the substances were exposed to the films for eighteen hours at 53° C. The films in direct contact with the substance were the only ones affected. Although quite definite the



reduction of the silver was too slight for reproduction of the appearances in a figure.

#### F.—Other Substances.

It is unnecessary to give in detail the experiments that have been made with metallic arsenic, arsenious oxide, betel nut and coal, for in no case was a difference observed in the rate of discharge of the electroscope which was outside the limits of error of observation (about  $2\frac{1}{2}$  per cent. on one complete observation), nor was any small difference that obtained found to be constant. The specimens of these substances, therefore, must be regarded as without influence on the rate of discharge of an electroscope under the conditions, at least, of the present research.

*Effects on Photographic Plates.*—Coal (six and a half months' exposure) showed no reduction of the silver. Metallic arsenic and arsenious oxide (thirty-six days at  $18^{\circ}\text{C}$ ) showed a zone of reduction of silver, and the reduction was greater in the neighbourhood of the arsenious oxide; exposed for eighteen hours at  $53^{\circ}\text{C}$  metallic arsenic showed no reduction of silver either when in close proximity or in actual contact with the photographic film. Betel nut was examined photographically for thirty-six days at  $18^{\circ}\text{C}$ , for eighteen hours at  $53^{\circ}\text{C}$ , and for eleven days at  $-3^{\circ}\text{C}$ . The following relations of substance and photographic film were investigated:—the cut surface of the nut in contact with the film; at a little distance from the film without intervening substance; the nut separated from the film by thick glass; by a film of glass  $\cdot 015\text{ mm.}$  in thickness; by a thick celloidin film; by a thin celloidin film, both freshly prepared and old; by tin foil; and by thin gutta percha tissue. Actinic effects were obtained in the form of a picture of the dark portions of the cut surface of the nut at  $-3^{\circ}\text{C}$ , at  $18^{\circ}\text{C}$ , and at  $53^{\circ}\text{C}$ , when the substance was in contact with the film, and the distinctness of the figure appeared to be greater when the nut had been recently cut. Under other conditions than contact with the photographic film the substance gave evidence of actinic effect only with a *freshly* prepared celloidin film between it and the photographic film; or at a short distance from the photographic film when a recently cut surface of the nut was exposed. No actinic

effect was produced by betel nut through glass, well-dried celloidin, gutta percha tissue, or tinfoil.

In the preceding experiments evidence has been given that introduction of various substances into the electroscope is followed by a retarded rate of discharge of the electricity on the gold leaves. I have sought to eliminate the possibility that the retarding effect depends upon induction by the experiments made with the substances enclosed within an aluminium box or covered with an aluminium cap and resting upon the metal base of the electroscope.

In the following sections the nature of this retardation is investigated more closely and, in certain directions, with the aid of definite radio-active substances. The reason for this part of the research is that it was desirable to determine whether the retardation was due (1) to obstructive properties of the substance, or (2) to approximation of the substance to the gold leaves, or (3) showed a fundamental distinction between the substances under investigation and recognised radio-active substances.

#### **The Obstructive Properties of the Substance.**

In order to investigate whether the reduced rate of discharge were due to the obstructive properties of the substance whereby it prevented certain discharging influences possibly resident in the metal base from reaching the gold leaves, experiments were directed to this end. In view of the high atomic weight of lead it was considered possible that it possesses discharging properties. Although the experiments do not decide this point they make it clear that the discharge-retarding character of the substances under consideration does not depend entirely upon obstruction of discharging influences from the lead base upon which they are placed.

In these experiments a number of small discs of paraffin were prepared about 1 mm. in thickness and 6 cm. in diameter. These discs were all cut out by the same instrument from a layer of paraffin that had been poured out on a level glass plate and had been allowed to cool. By superposing discs it was possible to increase the obstructive effect of the paraffin without increasing appreciably the surface exposed to the leaves.

## EXPERIMENT 80.

	Discharge in 24 hours.
Electroscope with aluminium box . . .	$7\frac{1}{2}$ mm.
With one paraffin disc in aluminium box . . .	7 "
„ two paraffin discs „ „ . . .	$6\frac{3}{4}$ "
„ three „ „ „ . . .	$6\frac{3}{4}$ "
„ four „ „ „ . . .	7 "

From the above experiment it appeared that two discs of paraffin completely produced all the obstructive effect of the paraffin on any discharging influences that might be coming from the lead base. It is clear, however, that no evidence as to the possession by paraffin of a special retarding power residing in itself is given by this experiment. Nevertheless, it forms a basis whereby other substances can be tested and *mutatis mutandis* when the obstructive power of another substance has been determined the question of a specific influence residing in paraffin can be decided. The point is an important one and consequently the argument on which it rests will be given.

If we consider such a substance as uranium which is certainly discharging, any obstructive effect that it may have on rays possibly coming from the lead base of the electroscope is negligible because the influences in question from the uranium are far more numerous than those from the lead. But if we are examining some substance of a doubtful low radio-activity and are at the same time uncertain whether the base is radio-active also, it is impossible to determine whether the substance under investigation possesses a radio-activity of its own *unless it intensifies the rate of discharge*. In other words, to examine whether a substance is a discharging substance it must be examined on a metal base which is completely neutral or at least is itself discharging. On the hypothesis that the base contained discharge-retarding influences these might entirely counteract definite discharge-accelerating influences proceeding from the substance under investigation. Similarly it is necessary to examine a substance which apparently retards the discharge of the electroscope either on a base which is completely neutral or on one which also shows discharge-retarding properties, e.g. pitch. There are four possible explanations of this retarding action. (1) The substances may obstruct

discharging influences proceeding from the lead base; (2) they may possess specific discharge-retarding properties; (3) both (1) and (2) may obtain; (4) they may possess feeble discharging properties themselves, but may obstruct more powerful influences proceeding from the lead base. If then discs of pitch be superposed until the rate of discharge becomes constant, the obstructing effect of the pitch is increased (while any hypothetical influence proceeding from the pitch remains constant) until all influences from the lead base which cannot pass through pitch are cut out. The discharge then obtained consequently represents the effect of the lead electroscope *less* the part beneath the pitch discs, and with the addition of any influences that may proceed from the pitch. Now place a single disc of paraffin above the pitch discs. The result may be (1) no alteration in the rate of discharge; (2) an acceleration of discharge; or (3) a retardation of discharge. If there be no alteration in the rate of discharge it is likely that the paraffin is without specific influences. If the discharge be accelerated this may be because the paraffin possesses discharging properties or because the substance is brought nearer to the gold leaves, a question easy to determine. If the discharge be still further retarded the result may be due (1) to the possession by the paraffin of definite discharge-retarding powers; (2) the cutting off of influences from the lead which the pitch could not cut off, or (3) the cutting off of discharging influences proceeding from the pitch. The possibilities (2) and (3) can be determined by superposing paraffin discs on the one already under examination.

## EXPERIMENT 81.

	Discharge in 24 hours.
Electroscope alone . . . . .	$8\frac{3}{4}$ mm.
With one pitch disc on metal base . . . . .	$8\frac{1}{2}$ "
„ two pitch discs on metal bases . . . . .	8 + "
„ four „ „ „ „ . . . . .	8 + "
„ five „ „ „ „ . . . . .	8 + "
Hence two pitch discs give the lowest reading.	
Electroscope with two pitch discs and one superposed paraffin disc . . . . .	$7\frac{1}{2}$ "
With two superposed paraffin discs . . . . .	$7\frac{1}{4}$ "
„ three „ „ „ „ . . . . .	$7\frac{1}{4}$ "



## EXPERIMENT 82.

Similar to the above but carried out throughout with the pitch and paraffin discs enclosed in an aluminium box.

	Discharge in 24 hours.
Electroscope with empty aluminium box on base . . . . .	$7\frac{1}{2}$ mm.
With one pitch disc in aluminium box . . . . .	$6\frac{3}{4}$ „
„ two pitch discs in aluminium boxes . . . . .	$6\frac{3}{4}$ „
Hence one pitch disc gives lowest reading.	
Electroscope with one pitch disc and one superposed paraffin disc in aluminium box . . . . .	$6\frac{1}{4}$ „
With two superposed paraffin discs . . . . .	$6\frac{1}{4}$ „

From these experiments it appears that the retarding properties of paraffin wax do not depend, at all events entirely, upon obstruction of discharging influences proceeding from the base but reside in the paraffin wax itself.

**The Effect on the Rate of Discharge of the Electroscope produced by Approximation of a Substance to the Gold Leaves.**

In placing a substance within the electroscope it is clear that one of the altered conditions brought about is a diminution of the distance between the leaves and the base of the system. In order to determine the effect of such an alteration two sets of experiments were undertaken in one of which a varying number of glass discs, in the other lead discs, were interposed between the base of the electroscope and the gold leaves. The thickness of the individual discs was in each case  $\frac{1}{8}$  in. The disc actually exposed to the leaves in each half of the experiment was always the same.

## EXPERIMENT 83.

	Discharge in 24 hours.
Electroscope without glass discs on base . . . . .	$11\frac{1}{4}$ mm.
„ with one „ „ . . . . .	$10\frac{3}{4}$ „
„ „ two „ „ . . . . .	11 „
„ „ three „ „ . . . . .	$10\frac{1}{4}$ „
„ „ one „ „ . . . . .	$10\frac{1}{2}$ „
„ „ one lead disc „ „ . . . . .	$11\frac{1}{4}$ „
„ „ two „ „ . . . . .	11 „
„ „ three „ „ . . . . .	$9\frac{3}{4}$ „

From the above experiment it appears that the rate of discharge of the electroscope diminishes somewhat as the substance is brought closer to the gold leaves. But in no case among the experiments 1 - 79 was the layer of substance under investigation greater than  $\frac{1}{8}$  in. in thickness and, in addition, the upper surface of the aluminium covers themselves was only  $\frac{5}{16}$  in. above the base. While, therefore, it is possible that some portion of any observed retardation caused by a substance under investigation may have been due to the diminished distance between the leaves and the base of the system, such portion can only be called into question in the case of investigations with the substance uncovered and even then does not amount to more than  $\frac{1}{4}$  mm. at most. In the case of investigations made with the substance covered by an aluminium lid the question does not arise, since the distance between the leaves and the aluminium cover was the same whether the substance was beneath or not.

**On the Electrical Changes Manifested by Aluminium and Paraffin Discs after Proximity to certain Recognised Radio-active Substances.**

In the following experiments the radio-active substance was placed direct upon a metal base that was completely earthed, and the disc was supported on lead uprights over the radio-active substance and at a distance of about 2 mm. from it. A lead cover, which was in contact with the upper surface of the disc, enclosed the whole and rested on the metal base supporting the radio-active substance. The discharging power of the discs was determined before bringing them into proximity with the radio-active substances, and was compared with corresponding values obtained afterwards.

**EXPERIMENT 84.**

*All Electroscopes charged with Positive Electricity.*

**URANIUM NITRATE.**

	Aluminium Disc.	Paraffin Disc.
Before proximity .	10 mm.	8 $\frac{1}{2}$ mm.
After proximity :		
First 48 hours .	9 mm. (retarded)	8 $\frac{1}{2}$ mm. (same).
Second 48 hours .	Exposed to air.	
Third 48 hours .	9 $\frac{3}{4}$ mm. (still retarded)	9 $\frac{1}{2}$ mm. (accelerated).
Fourth 48 hours .	Exposed to air.	
Fifth 48 hours .	9 $\frac{3}{4}$ mm. (still retarded)	9 mm. (still accelerated).

EXPERIMENT 84.—*continued.*

## THORIA.

	Aluminium Disc.	Paraffin Disc.
Before proximity.	12 mm.	8½ mm.
After proximity :		
First 48 hours .	13½ mm. (accelerated)	10¾ mm. (accelerated).
Second 48 hours .	Exposed to air.	
Third 48 hours .	10¾ mm. (retarded)	11 mm. (still accelerated).
Fourth 48 hours .	Exposed to air.	
Fifth 48 hours .	11¾ mm. (still retarded)	12¾ mm. (still accelerated).

## PITCHBLEND.

Before proximity.	10 mm.	8½ mm.
After proximity :		
First 48 hours .	10 mm. (same)	10¼ mm. (accelerated).
Second 48 hours .	Exposed to air.	
Third 48 hours .	9½ mm. (retarded)	9½ mm. (still accelerated).
Fourth 48 hours .	Exposed to air.	
Fifth 48 hours .	9¼ mm. (still retarded)	9 mm. (still accelerated).

## RADIUM.

Before proximity.	12 mm.	8½ mm.
After proximity :		
Immediately .	Rate of 1,728 mm. (accelerated).	Rate of 864 mm. (accelerated).
Second period (43 hours)	Exposed to air.	
Third period .	Rate of 28 mm. (still accelerated).	Rate of 54 mm. (still accelerated).
Fourth period (48 hours)	Exposed to air.	
Fifth period (48 hours)	13½ mm. (still accelerated)	Rate of 33 mm. (still accelerated).
Sixth period (48 hours)	Exposed to air.	
Seventh period. (48 hours)	13½ mm. (still accelerated)	Rate of 22 mm. (still accelerated).
Eighth period (6 days)	Exposed to air.	
Ninth period . (48 hours)	13½ mm. (still accelerated)	Rate of 20 mm. (still accelerated).
Tenth period (4 days)	Exposed to air.	
Eleventh period (48 hours)	12½ mm. (still accelerated)	Rate of 18 mm. (still accelerated).

*Discharge of Electroscopes alone in 48 Hours.\**

No. of Electroscope	I.	II.	III.	IV.
Before above series .	9½ mm.	9½ mm.	11½ mm.	10 mm.
After " "	9¾ mm.	10 mm.	11½ mm.	11 mm.

\* Electroscopes I and II were used for investigating, respectively, the aluminum and paraffin discs exposed to uranium nitrate or pitchblende. Electroscopes III and IV were reserved for the aluminium and paraffin discs, respectively, exposed to thoria or to radium.

From these experiments it appears that the aluminium and paraffin discs were altered in opposite directions, for whereas the aluminium discs, after proximity to a radio-active substance, discharged an electroscope charged with positive electricity at a slower rate than before proximity, paraffin discs under identical circumstances discharged the electroscope at a more rapid rate.

By dividing up the periods of 48 hours into two periods of 24 hours and comparing the rates of discharge of the electroscope under the various conditions indicated in the present section, a clearer view is obtained of the processes at work. In the following table are given the differences in the amount of discharge of the electroscope between the unexposed and the exposed discs. The discs exposed to radium are omitted from this table, but the *tendencies* shown by them conform in all respects with those shown by the other radio-active substances.

*Table showing the differences (in 24-hour periods) in power of discharging an electroscope charged with positive electricity by aluminium and paraffin discs before and after approximation to uranium nitrate, thorium, or pitchblende for 48 hours.*

	Aluminium Disc.	Paraffin Disc.
<b>URANIUM.</b>		
First observation . . .	Retardation $\frac{3}{4}$ mm.	Retardation $\frac{1}{2}$ mm.
Second " . . .	" $\frac{1}{4}$ mm.	Acceleration $\frac{1}{2}$ mm.
Third " . . .	" $\frac{1}{4}$ mm.	" 0
Fourth " . . .	0	" 1 mm.
Fifth " . . .	Retardation $\frac{1}{4}$ mm.	" $\frac{1}{2}$ mm.
Sixth " . . .	0	" $\frac{1}{4}$ mm.
<b>THORIA.</b>		
First observation . . .	Acceleration $1\frac{3}{4}$ mm.	Acceleration $1\frac{1}{2}$ mm.
Second " . . .	Retardation $\frac{1}{2}$ mm.	" $\frac{3}{4}$ mm.
Third " . . .	" $1\frac{1}{4}$ mm.	" $1\frac{1}{2}$ mm.
Fourth " . . .	0	" 1 mm.
Fifth " . . .	Retardation $\frac{1}{4}$ mm.	" $2\frac{3}{4}$ mm.
Sixth " . . .	0	" $1\frac{1}{2}$ mm.
<b>PITCHBLEND.</b>		
First observation . . .	Retardation $\frac{1}{2}$ mm.	" $\frac{3}{4}$ mm.
Second " . . .	Acceleration $\frac{1}{4}$ mm.	" 1 mm.
Third " . . .	Retardation $\frac{1}{2}$ mm.	" $\frac{1}{4}$ mm.
Fourth " . . .	" $\frac{1}{4}$ mm.	" $\frac{1}{4}$ mm.
Fifth " . . .	" $\frac{3}{4}$ mm.	0
Sixth " . . .	0	" $\frac{1}{2}$ mm.

Viewed in this manner, it appears that one has to distinguish between a temporary and a more or less permanent



change in the discs. During the first period of 24 hours both discs may show an alteration of the rate of discharge in the same direction, but after that time the aluminium disc uniformly manifests a retarding power, while the paraffin disc uniformly manifests an accelerating power when the leaves are charged with positive electricity.\*

**On the Electrical Changes Manifested by Aluminium and Paraffin Discs after Prolonged Contact with certain Recognised Radio-active and other Substances.**

In the following experiments the radio-active substance lay between the paraffin and aluminium discs, and the base and lid of the lead box were in wide contact with the free surfaces of the paraffin and aluminium discs respectively. The lead boxes containing the radio-active substance and the discs were placed on an earthed metal base.

The experiments were partly carried out by comparing the lengths of time that it took for an exposed disc and an exactly similar unexposed (control) disc to discharge the gold leaves over a fixed quarter of an inch and partly by comparing the rates of discharge of the same disc before and after contact with the radio-active substance.

**EXPERIMENT 85.**

*Leaves charged with Positive Electricity.*

	Aluminium Disc.	Paraffin Disc.
<b>GALLSTONE (<i>Simmons</i>).</b>	Minutes.	Minutes.
Control disc . . .	13.25	19.83.
Exposed „ . . .	12.87 (accelerated)	21.62 (retarded).
<b>THORIA.</b>		
Control disc . . .	14.00	23.42.
Exposed „ . . .	13.12 (accelerated)	25.75 (retarded).
<b>URANIUM NITRATE.</b>		
Control disc . . .	15.69	29.60.
Exposed „ . . .	14.83 (accelerated)	27.67 (accelerated).
<b>PITCHBLEND.</b>		
Control disc . . .	31.42	27.14.
Exposed „ . . .	27.17 (accelerated)	29.75 (retarded).

\* Subsequent re-examination of the electrical condition of an aluminium disc after proximity to uranium thoria or pitchblende confirms the general statement made in the text that the disc has acquired retarding properties. The subject is still under investigation. May 16th, 1906.

EXPERIMENT 85.—*continued.*

		Loss in 24 hours.	Loss in 24 hours.
GALLSTONE ( <i>Simmons</i> ).			
Before contact		5 $\frac{3}{4}$ mm.	5 mm.
After contact :			
First period (24 hours)	8 $\frac{7}{8}$ mm. (accelerated)	3 $\frac{1}{2}$ mm. (retarded).	
Second period (24 hours)	9 mm. (accelerated)	3 $\frac{1}{4}$ mm. (retarded).	
Third period (8 days)		Exposed to air.	
Fourth period (24 hours)	5 $\frac{3}{4}$ mm.	4 $\frac{1}{2}$ mm. (retarded).	
THORIA.			
Before contact		6 $\frac{3}{4}$ mm.	5 $\frac{1}{2}$ mm.
After contact :			
First period (24 hours)	9 mm. (accelerated)	Rate of 30 $\frac{1}{2}$ mm. (accelerated).	
Second period (24 hours)	9 $\frac{1}{2}$ mm. (accelerated)	Rate of 35 mm. (accelerated).	
Third period (8 days)		Exposed to air.	
Fourth period (24 hours)	9 mm. (accelerated)	Rate of 30 mm. (accelerated).	

These experiments are the means of many that have been made, with the exception of the last two (i.e. the aluminium and paraffin discs with gallstone "*Simmons*" and thoria), in each of which cases a single complete set of observations is given.

It is seen that the aluminium discs in all cases have become altered in such a way that they discharge the electroscope more rapidly than before contact with the radio-active substance. The paraffin discs have also become altered, but in such a way that they retard the discharge of the electroscope. This retardation by the exposed paraffin disc is not universal, for two instances are shown of an acceleration by the exposed paraffin disc. It is possible that this acceleration by the exposed paraffin disc is wholly or in great part accidental, and due to adhesion of some of the radio-active substance itself to the disc. In support of this view is the fact that in cases (uranium nitrate) in which the paraffin disc was washed for about half a minute under a stream of cold tap-water, the greater part of the acceleration disappeared.

The differences between the properties acquired by the aluminium and paraffin discs according as they were subjected to "proximity" or to "contact" with the radio-active substance are remarkable. It is possible that the "proximity" effects are tantamount to very late "contact" effects. At all events in the case of the aluminium discs more recent experiments have shown that a transient accelerating character,

such as was found on the aluminium disc after "proximity" to thoria, is also met with after proximity to uranium and pitchblende, but may be marked by the retarding property.

**On the Rate of Discharge of an Electroscope by certain Recognised Radio-active Substances, directly, and covered by Aluminium or Paraffin Wax, according as the Leaves of the Electroscope are charged with Positive or Negative Electricity.**

It is known that radio-active substances discharge an electroscope, whether it is charged with positive or negative electricity, but in the light of the preceding experiments it became necessary to try and determine whether the rates of discharge of the substances themselves are identical with positive and negative charges on the leaves under varying conditions.

EXPERIMENT 86.

(1) The rates of discharge of the uncovered radio-active substance—

Substance.	Positive Electricity.	Negative Electricity.
Uranium nitrate .	{ 8 min. 42 sec. 8 min. 21 sec.	8 min. 30 sec. 8 min. 20 sec.
Thoria . . .	{ 1 min. 53 sec., 1 min. 54 sec. 1 min. 52 sec. (twice). 1 min. 51 sec. (twice).	1 min. 47 sec., 1 min. 53 sec. 1 min. 54 sec., 1 min. 51 sec. (three times).
Pitchblende .	{ 51 sec. (three times). 52 sec. (three times).	51 sec., 53 sec., 52 sec. (four times).

(2) The rates of discharge of the substance covered by a lid of paraffin wax which is not in contact with the substance—

Substance.	Positive Electricity (Discharge per hour).	Negative Electricity (Discharge per hour)
Uranium nitrate . . .	2.06 mm.	2.62 mm.
Thoria . . . . .	2 mm.	2.45 mm.
Radium-barium chloride .	521 mm. (rate of)	574 mm. (rate of)
Pitchblende . . . . .	12 mm.	13 mm.

(3) The rates of discharge of the substance covered by a lid of aluminium which is not in contact with the substance—

Substance.	Positive Electricity (Discharge per hour).	Negative Electricity (Discharge per hour).
Uranium nitrate . . .	7.67 mm.	8.1 mm.
Thoria . . . . .	7.11 mm.	8.4 mm.
Radium-barium chloride .	3046 mm. (rate of)	2640 mm. (rate of)
Pitchblende . . . . .	33 mm. (rate of)	31.7 mm. (rate of)

The experiments made with the uncovered substances show differences so small that they come within the range of experimental error, and it would not be safe to conclude that differences obtain according as the leaves are charged with positive or negative electricity.

There is no doubt, however, that a difference shows itself when the radio-active substances are covered with a lid of paraffin wax or of aluminium, according as the sign of the electrical charge on the gold leaves is  $+$  or  $-$ . Into the real cause of this difference it is impossible to enter here, especially as it is uncertain, in view of the "proximity" experiments that have been given earlier, whether the results obtained indicate the action of the radio-active substance itself or the secondary action of the paraffin or aluminium lid induced by the proximity of the radio-active substance. Nevertheless, it is noteworthy that whereas all the substances investigated showed a more rapid discharge of the gold leaves if they were charged  $-$ , when the radio-active substance was covered with a lid of paraffin, this was not the case when the radio-active substance was covered with a lid of aluminium. The figures given in (2) and (3) above are the means of several estimations in each case.

### III.—SUMMARY AND CONSIDERATION OF RESULTS.

The results that have been obtained may be summarised as follows:—

- (1) Clay pipes accelerated the discharge of an electroscope, but were without actinic effect upon a photographic plate.
- (2) Paraffin wax retarded the discharge of an electroscope, and was without actinic effect upon a photographic plate.
- (3) Cholesterin gallstones retarded the discharge of an electroscope, and certain specimens exerted actinic effects upon a photographic plate. Most specimens of pure pigment gallstones were without actinic action, but one example showed marked actinic action. The electrical phenomena manifested by pure pigment gallstones have not been sufficiently worked out to admit of a conclusion being drawn.
- (4) One sample of soot gave conflicting electrical results, and was without actinic action; the other sample of soot



retarded the discharge of the electroscope and yielded evidence of actinic action.

(5) Betel nut, metallic arsenic, and arsenious oxide gave evidence of actinic effects under various conditions, but were apparently without effect upon the rate of discharge of an electroscope.

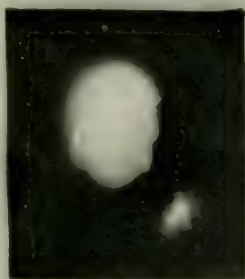
(6) Aluminium and paraffin discs that had been kept for some hours in proximity with recognised radio-active substances showed an acquired power of retarding and accelerating the discharge of a positively charged electroscope, respectively.

(7) Aluminium and paraffin discs that had been kept in contact with recognised radio-active substances for some hours showed acquired electrical properties the converse of those acquired as the result of proximity to the radio-active substances.

(8) Gallstone "Simmons" showed the power of inducing similar changes in aluminium and paraffin discs as are produced by recognised radio-active substances when examined under conditions of "contact."

(9) Recognised radio-active substances were found to discharge an electroscope at different rates when the leaves were charged + and —.

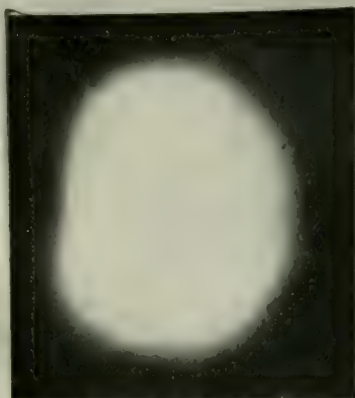
*Consideration of the Electrical Results.*—The accelerating properties that were found to reside in all the samples of clay pipes, and possibly in one sample of soot, are in marked contrast to the retarding effects that were observed with gallstones, paraffin wax, pitch, and the pure sample of soot. The property of accelerating the discharge of an electroscope under the various conditions introduced into the research is in accord with the electrical properties of recognised radio-active substances and raises no difficulty. The matter is far otherwise with the retarding effects, and they must be regarded as still unexplained. In view of the fact that they were manifested even when the substance was enclosed within an aluminium box, it is impossible to regard them as due to induction, and it is equally difficult to regard them as due to the presence of a minute electrical charge upon the substance. It has been made clear also, that they are not due to obstruction of accelerating influences normally pro-



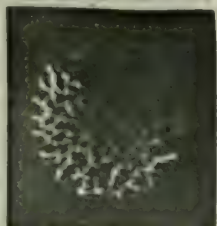
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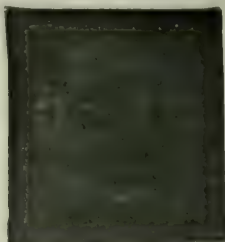
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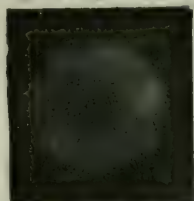
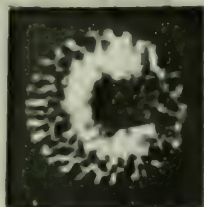
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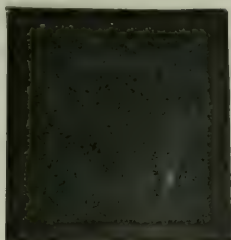
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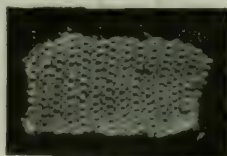
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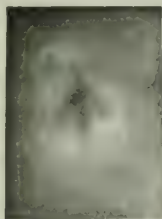
1.  $A \cap B = \{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100\}$   
 2.  $A \cap C = \{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100\}$   
 3.  $A \cap D = \{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100\}$   
 4.  $A \cap E = \{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100\}$



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ceeding from the base of the electroscope, or to diminution of the capacity of the electroscope, or to approximation of the substance to the gold leaves. Further, evidence has been given that recognised radio-active substances are capable, under certain conditions, of including retarding properties in substances with which they are brought into relation, and that this property is shared by one of the specimens of gallstone examined.

*Consideration of the Photographic Results.*—Although evidence has been given of actinic action by some of the substances investigated, a sharp distinction between the action of the substances and recognised radio-active substances must be drawn, for none of the solid substances usually associated with carcinoma produced actinic effects when separated from the photographic film by a thin screen, except under special conditions (betel nut). It is clear, therefore, that the substances investigated were devoid of  $\beta$  and  $\gamma$  rays, but whether the undoubted actinic action of such a substance as the pure cholesterin gallstone or betel nut is due to  $\alpha$ -rays it is impossible to say. It is equally possible that it may be due to the action of such a substance as hydrogen peroxide, as Dr. Russell suggested to me. An attempt was made to distinguish between radio-active and hydrogen peroxide action by carrying out the photographic work at different temperatures, but without success.

*To sum up.*—Although the substances, clay pipes, paraffin wax, pitch, gallstones, and soot have certain properties, either electrical or photographic, which are apparently identical with properties possessed by recognised radio-active substances, it is impossible to regard them as radio-active substances, at least in the present acceptance of that term. Nor is it, as yet, possible to say whether the property of retarding the discharge of an electroscope which has been shown to exist under a variety of conditions, is a specific inherent property that is at present unrecognised.

NOTE.—I beg to tender my thanks for criticism and advice to Sir W. Ramsay, F.R.S., to Dr. Russell, F.R.S., concerning the photographic portion of the work, and to my colleagues, Dr. Kellas and Mr. Lyster, concerning the electrical portion.







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